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Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies.

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OBJECTIVE: Therapeutic strategies for rheumatoid arthritis (RA) have been evolving from the traditional "pyramid" approach toward one based upon early and sustained use of disease-modifying antirheumatic drugs (DMARDs), in the hope of improving long-term health outcomes. However, few data to have been presented to document the effects of this approach. We sought to directly assess associations between consistent DMARD use and long-term functional outcomes. METHODS: We studied 2,888 RA patients who were followed up prospectively for up to 20 years (average 9 years) at 8 databank centers. The independent variable was the proportion of patient encounters that resulted in treatment with > or = 1 DMARD (hydroxychloroquine, sulfasalazine, auranofin, intramuscular gold, D-penicillamine, methotrexate, and/or azathioprine). The dependent variable was each patient's last recorded Disability Index value from the Health Assessment Questionnaire (HAQ). RESULTS: Increased DMARD use was strongly associated with better long-term Disability Index values ($P < 0.0001$). The association was strengthened when restricted to more seriously affected (rheumatoid factor (RF)-positive) patients. The magnitude of the effect, unadjusted, was a difference of 0.53 HAQ Disability units (scale 0-3) between 100% DMARD use and 0%. Correlation coefficients ranged up to 0.26. Effects were similar for all disease duration periods (0-4, 5-9, 10-14, 15-19, and 20+ years). "Control" correlations, with variables computed to represent the proportion of time in which patients were taking either nonsteroidal anti-inflammatory drugs or prednisone, failed to show positive associations. A multiple linear regression model, which controlled for age, disease duration, sex, RF positivity, proportion of visits under a prednisone regimen, and initial disability level, included the proportion of time in which patients were taking DMARDs ($P < 0.0001$), with a model R2 of 0.54. These results were obtained despite an adverse selection bias in which more severely affected individuals were given DMARDS more frequently, and despite absence of data on drug use early in the disease course of many patients. Thus, these results, which suggest up to a 30 percent reduction in long term disability with consistent DMARD use, are most likely conservative. CONCLUSION: An association between consistent DMARD use and improvement in long-term functional outcomes in RA is supported by these data.

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Therapeutic strategies in early rheumatoid arthritis.

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Rheumatoid arthritis (RA) therapy rests primarily on the use of disease-modifying antirheumatic drugs (DMARDs). It has been unequivocally shown that DMARD therapy early in the course of RA retards progression of damage and disability to a larger degree compared with delayed institution; the most effective DMARD is methotrexate (MTX). Moreover, combination therapy including intermediate to high doses of glucocorticoids and combinations of MTX with tumour necrosis factor blockers are more effective than monotherapies. However, early DMARD treatment requires early referral of patients and early diagnosis. This is hampered by the current lack of classification criteria for early RA, since the aim is to prevent destruction from occurring, while RA is typically characterized by the presence of erosions. Novel treatment strategies and therapeutic agents allow us to aim for remission rather than improvement of disease activity. Whether a 'window of opportunity' exists during which effective therapy might lead to cure is still an open issue and will be the focus of clinical trials in the near future.

Publication Types:

- Review

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EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)

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EXTENDED REPORT

EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)

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Objective: To formulate EULAR recommendations for the management of early arthritis.

Methods: In accordance with EULAR's "standardised operating procedures", the task force pursued an evidence based approach and an approach based on expert opinion. A steering group comprised of 14 rheumatologists representing 10 European countries. The group defined the focus of the process, the target population, and formulated an operational definition of "management". Each participant was invited to propose issues of interest regarding the management of early arthritis or early rheumatoid arthritis. Fifteen issues for further research were selected by use of a modified Delphi technique. A systematic literature search was carried out. Evidence was categorised according to usual guidelines. A set of draft recommendations was proposed on the basis of the research questions and the results of the literature search.. The strength of the recommendations was based on the category of evidence and expert opinion.

Results: 15 research questions, covering the entire spectrum of "management of early arthritis", were formulated for further research; and 284 studies were identified and evaluated. Twelve recommendations for the management of early arthritis were selected and presented with short sentences. The selected statements included recognition of arthritis, referral, diagnosis, prognosis, classification, and treatment of early arthritis (information, education, non-pharmacological interventions, pharmacological treatments, and monitoring of the disease process). On the basis of expert opinion, 11 items were identified as being important for future research.

Conclusions: 12 key recommendations for the management of early arthritis or early rheumatoid arthritis were developed, based on evidence in the literature and expert consensus.

The definition of rheumatoid arthritis is sometimes imprecise, but the term is normally used to describe a symmetrical, persistent, and destructive polyarthritis often associated with rheumatoid factor or with positive results in tests for anti-cyclic citrullinated peptide (anti-CCP) antibodies. An early diagnosis is complicated by the absence of specific tests and diagnostic criteria.[1] In practice, early inflammatory arthritis is often undifferentiated.[2] Early arthritis may develop into established rheumatoid arthritis or into another definite arthropathy, may resolve spontaneously, or may remain undifferentiated. For an improved evaluation of the diagnosis and outcome in arthritis, it has been proposed that the first step should be to recognise the presence of inflammatory arthritis, the next should be to exclude definite diagnoses of arthritis (for example, systemic lupus erythematosus (SLE), psoriatic arthritis, seronegative spondylarthropathies, and so on), and the final step should be to estimate the risk of developing persistent or erosive irreversible arthritis and to propose an optimal therapeutic strategy.[2 3] Although the prognosis of early arthritis is still a difficult issue to address, a combination of clinical biological and radiographic indices may help to predict the outcome of arthritis with acceptable accuracy.

In the past few years the development of effective new treatments and the validation of new concepts have highlighted the need to develop guidelines for the management of early arthritis. New disease modifying antirheumatic drugs (DMARDs) and DMARD combinations have shown their ability to slow disease progression.[4–7] Furthermore, biological treatments have resulted in rapid and sustained disease control, associated with an impressive prevention of joint destruction.[8–10] There is now a body of evidence about early rheumatoid arthritis to support the very early use of effective DMARDs—preferably before the first radiographic evidence of erosions—to prevent further joint damage and disability.[11–13] The assessment and close monitoring of patients with early arthritis seem crucial for the optimisation of therapeutic strategies.[7 14] In addition, management of early arthritis includes more than drug treatment alone, and an ideal treatment proposal should be based on an appropriate assessment of the prognosis in the individual case.

A potential limitation is that management of early rheumatoid arthritis varies widely among countries, doctors (rheumatologists or general practitioners), and settings (university hospital, private practice, and so on), owing to differences in

Abbreviations: ACR, American College of Rheumatology; ASPIRE, Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ESCISIT, European Standing Committee for International Clinical Studies Including Therapeutics; EULAR, European League Against Rheumatism; RCT, randomised controlled trial; TEMPO, Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; TICORA, Tight Control for Rheumatoid Arthritis study; TNF, tumour necrosis factor

culture, health care reimbursement policies, patients' and physicians' preferences, and similar issues.

The objective of this task force was to formulate, and obtain consensus on, a set of recommendations aiming at improving the management of early arthritis. The European League Against Rheumatism (EULAR) standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations[15] has served as a framework to achieve this goal.

METHODS

The EULAR standardised operating procedures prescribe a discussion among experts in the field about the focus, the target population, and an operational definition of the term "management", followed by consensus building based on currently available literature (evidence based), as well as on expert opinion, in order to arrive at a consensus on a set of recommendations.[15] An international expert committee should be formed as a platform for these discussions.

The expert committee

The expert committee comprised 14 rheumatologists and one research fellow (CL) from 10 European countries. All these experts have been involved in early arthritis clinics or early arthritis trials, or both, for many years. After discussion, the group voted to define the focus of the process (early undifferentiated arthritis, with a certain propensity to become persistent and erosive arthritis), and the target population (rheumatologists, GPs, medical students), and to obtain an operational definition of the term "management" ("All organisational, diagnostic, medical and educational procedures related to patients seeking help for arthritis of a peripheral joint").

Fifteen specific issues for further research were selected by use of a modified Delphi technique. The selected topics included recognition of arthritis, referral, diagnosis, prognosis, classification, information, education, non-pharmacological interventions, pharmacological treatments, and monitoring of the disease process (table 1). These research questions were adjusted for further literature research if appropriate, and key index terms were derived by three of us (BC, RL, CL).

Evidence based approach

A systematic search of PubMed, Medline, Embase, CINAHL, and the Cochrane library was carried out. All publications in English language up to January 2005 were included. A further selection was based on reading the title or the abstract. As the topics varied widely, no systematic scoring system was used.

Categories of evidence were applied according to Shekelle *et al*.[16] They include a hierarchy of evidence in descending order by study design (table 2). Questions posed were answered with the use of the best available evidence. An estimation of treatment effect was assessed when possible, by calculating the effect size and 95% confidence interval (CI) for validated continuous outcome measures of disease activity and structural damage compared with placebo or active control. We considered an effect size around 0.2 as small, around 0.5 as moderate, and greater than 0.8 as large.

Expert opinion approach

The results of the literature search were summarised, aggregated, and disseminated to the expert committee with the accompanying levels of evidence. A set of 15 draft recommendations was prepared by three of us (BC, RL, CL), which was a compilation of the research questions (expert opinion) and the results of the literature search (evidence based). This set of draft recommendations formed the basis for discussion during a second meeting. After discussion, voting, and adjusting the formulation, the expert committee eventually arrived at 12 final recommendations for the management of early arthritis. Further, the expert committee proposed topics for a research agenda. The recommendations are presented in brief sentences. The strength of the recommendations, according to the category of evidence (table 3) and the knowledge of the experts, was proposed by two members of the committee (BC, RL), graded from A (highest) to D (lowest),[16] and ratified by the expert committee.

The relevance of the recommendations was checked according to the AGREE instrument (www.agreecollaboration.org).

Table 1 Selected research questions for a literature search

- What is the clinical presentation of early arthritis that a GP should recognise in order to refer to the rheumatologist?
- How early should patients with arthritis be referred to a medical specialist?
- What are the diagnostic procedures that need to be undertaken in order to confirm early synovitis?
- What are the minimum diagnostic procedures necessary in a patient with early arthritis in order to exclude other diseases?
- What are the prognostic procedures that need to be carried out in a patient with confirmed early arthritis?
- Can we substitute distinct disease classifications (rheumatoid arthritis, psoriatic arthritis) with prognostic eponyms such as "persistent" or "persistent and erosive"?
- What is the efficacy of non-pharmaceutical interventions compared to efficacy of drug treatment in early arthritis? (Note: most findings are in *established* rheumatoid arthritis.)
- How should information be given (route of administration) in early arthritis?
- Are NSAIDs (classical and/or coxibs) more efficacious (efficacy in relation to toxicity) than analgesics (including opioids) in early arthritis? (Note: there have been no trial in early arthritis.)
- Is there a place for (intra-articular and/or systemic) corticosteroids in the treatment of early arthritis?
- Is an early treatment start with DMARDs better than a delayed treatment start in early arthritis?
- Is aggressive treatment (for example, combination therapy with or without corticosteroids) better than less aggressive treatment (monotherapy) in early arthritis?
- Can an optimal starting point (for example, X weeks of arthritis) be defined in early arthritis? (Is the starting point dependent on the prognosis?)
- Can consensus be obtained with regard to the choice of DMARD strategies in early arthritis?
- Can consensus be obtained on whether or not disease activity, radiographic progression, and function should be monitored, and if yes, how (by what instruments) and how often?

DMARD, disease modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

RESULTS

Evidence based approach

The general search identified a large number of publications related to arthritis. After deleting publications and articles irrelevant to the research questions, 284 manuscripts were further evaluated. They included reports of meta-analyses, randomised controlled trials (RCTs), controlled trials, observational studies, comparative studies, case–control studies, cross

Table 2 Categories of evidence[16]

Ia Evidence from meta-analyses of randomised controlled trials
Ib Evidence from at least one randomised controlled trial
IIa Evidence from at least one controlled study without randomisation
IIb Evidence from at least one type of quasi-experimental study
III Evidence from descriptive studies, such as comparative, correlation, or case–control
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

sectional surveys, systematic reviews, and expert reports or opinions. As original publications about early arthritis or early rheumatoid arthritis were missing on some topics such as non-pharmacological treatment or symptomatic treatments, some publications relevant to established rheumatoid arthritis, including 10 Cochrane reviews, were also examined.

Assessment of propositions

Table 4 summarises the final set of 12 recommendations as proposed by the expert committee. The strength of each recommendation is presented in table 5. The recommendations are ordered by topic, with no weighting according to order.

The recommendations

Recommendation 1

> Arthritis is characterised by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more than one joint should be referred to and seen by a rheumatologist, ideally within six weeks after the onset of symptoms.

Although the level of evidence supporting the content of this recommendation is rather low (category III or IV), there was general agreement that a recommendation regarding the recognition of arthritis and about early referral should be included. Joint swelling not caused by trauma or bony swelling should suggest a diagnosis of early arthritis, preferably if it includes involvement of at least two joints, with or without morning stiffness of more than 30 minutes' duration, and/or involvement of metacarpophalangeal and/or metatarsophangeal joints.[17–19] Involvement of hand and foot joints is suggested by a positive "squeeze test"[18 20] (category III).

One systematic review,[21] several randomised controlled studies,[22–25] and a number of prospective observational studies[11–13 26] showed a better outcome of arthritis when treatment is started earlier. Evaluation of the impact of a delay in the start of treatment on the outcome of arthritis is difficult. From evidence in published reports and the clinical experience of the members of the committee, it was recommended that drug treatment by a rheumatologist should start within a relatively short period after the onset of complaints, which justifies to the committee the wording "ideally within six weeks" in this recommendation. Several comparative studies[27–33] have shown a better functional status and earlier DMARD start in cases treated by rheumatologists, which further supports the view that patients with clinical presentations suggestive of arthritis should be referred to a rheumatologist early.[18]

Recommendation 2

> Clinical examination is the method of choice for detecting arthritis. In doubtful cases, ultrasound, power Doppler, and MRI may be helpful in detecting synovitis.

Table 3 Strength of recommendations[16]

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendations from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category II or III evidence

The expert committee was unanimous in their view that clinical examination is still the gold standard in detecting synovitis. This does not mean that imaging methods are incapable of detecting synovitis, and may even do so with greater sensitivity. Ultrasonography and power Doppler techniques allow the assessment of synovitis, by detecting thickening of the synovial membrane of inflamed joints and bursae or tendon sheaths. Two controlled studies have suggested that ultrasonography is more sensitive than clinical examination for detecting synovitis in knee joints.[34 35] However, ultrasonography and power Doppler have hardly been used at all for detecting synovitis of the small joints of the hands and feet[36] (category III), and scientific evidence of the clinical value of ultrasonography in early arthritis is limited. In one controlled study and in a few comparative studies, MRI has been shown to be more sensitive than clinical examination and radiography for the detection of synovitis and erosions in early rheumatoid arthritis.[37–39] There is evidence that MRI findings (for example, synovitis, bone oedema, and bone erosions) may predict subsequent radiographic progression.[40 41] However, the level of evidence is rather low, and changes resembling mild synovitis or small bone erosions are occasionally found in the joints of healthy subjects, raising questions about the specificity of this technique.[42] Issues of standardisation and reliability of MRI have been addressed and are ongoing.

Altogether, the expert committee thought that MRI and ultrasonography are promising techniques that may become valuable in the diagnosis, prognosis, and therapeutic monitoring of early arthritis. However, their use is still experimental and sometimes controversial, and their merits in routine clinical practice have yet to be defined.

Recommendation 3

> Exclusion of other diseases than rheumatoid arthritis requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urinary analysis, transaminases, and antinuclear antibodies.

This recommendation is entirely expert based. As experimental evidence from appropriately designed clinical trials was unavailable, the group considered that "good clinical practice" and a "high level of training" sufficed to address this topic, so no literature search was carried out. In order to exclude patients in whom the arthritis has differentiated into diseases other than rheumatoid arthritis which may have a different prognosis and treatment (such as connective tissue diseases, reactive arthritis, infectious arthritis, and others), the group proposed that the minimum diagnostic procedures should include a careful history and clinical examination, a complete blood cell count, transaminase analysis, urinary analysis, and antinuclear antibody testing.

The diagnostic procedure may also include tests for uric acid and Lyme disease, parvovirus infection, urethral or cervical swab cultures, anti-bacterial serology, tests for hepatitis B or C, or chest *x* ray, according to the context and the country. Tests for erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP) antibodies were excluded here, as these tests are related to the extent of the inflammation and the (prognostic) severity of the arthritis rather than to other diagnoses.

Recommendation 4

> In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent

Table 4 Final set of 12 recommendations on the management of early arthritis based on both evidence and expert opinion

- Arthritis is characterised by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more than one joint should be referred to, and seen by, a rheumatologist, ideally within six weeks after the onset of symptoms.
- Clinical examination is the method of choice for detecting synovitis. In doubtful cases, ultrasound, power Doppler, and MRI might be helpful to detect synovitis.
- Exclusion of diseases other than rheumatoid arthritis requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urinary analysis, transaminases, antinuclear antibodies.
- In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent and erosive disease should be measured: number of swollen and tender joints, ESR or CRP, levels of rheumatoid factor and anti-CCP antibodies, and radiographic erosions.
- Patients at risk of developing persistent or erosive arthritis should be started with DMARDs as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatological diseases.
- Patient information concerning the disease and its treatment and outcome is important. Education programmes aimed at coping with pain, disability, and maintenance of work ability may be employed as adjunct interventions.
- NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status.
- Systemic glucocorticoids reduce pain and swelling and should be considered as adjunctive treatment (mainly temporary), as part of the DMARD strategy. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.
- Among the DMARDS, methotrexate is considered to be the anchor drug, and should be used first in patients at risk of developing persistent disease.
- The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies (DMARDs including biological agents).
- Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis.
- Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessments, ESR, and CRP. Arthritis activity should be assessed at one to three month intervals, for as long as remission is not achieved. Structural damage should be assessed by radiographs of hands and feet every 6 to 12 months during the first few years. Functional assessment (for example, HAQ) can be used to complement the disease activity and structural damage monitoring.

CRP, C reactive protein; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging.

and erosive disease should be measured: number of swollen and tender joints, ESR or CRP, level of rheumatoid factor and anti-CCP antibodies, and radiographic erosions.

After exclusion of diseases other than rheumatoid arthritis, the third step in the diagnostic procedure should be to try to determine the patients at risk of developing persistent or erosive arthritis. This prognostic typing was considered crucial to guide the optimal therapeutic strategy. Forty five studies that evaluated the prognostic factors in early arthritis (n = 5) or early rheumatoid arthritis (n = 40) were examined. They are all observational or case–control studies (category III). Most prognostic factors were analysed in a multivariate manner in these studies, so that their independent contribution could be tested. In many of the studies, the variable to predict (dependent variable) was radiographic progression. The presence of IgM or IgA rheumatoid factor,[20 43–59] high ESR or CRP level,[41 43 44 47 49 50 53 55 57 59] and early radiographic evidence of erosions,[20 43 44 49 52 54 56 58 61] according to most of the reports, independently predict long term radiographic progression. The number of swollen joints probably correlates better with radiographic progression than the number of tender joints.[20 44 46–49] Recently, several studies have shown that presence of anti-CCP antibodies is also an independent prognostic factor for radiographic progression in early arthritis and early rheumatoid arthritis.[20 54 60–64] The presence of HLA-DRB1*0401 and DRB1*0404 is also consistently associated with joint damage in different ethnic groups.[43 49 61] This association appears to be dose dependent, as patients with two rheumatoid arthritis associated genes show more radiographic evidence of destruction than those with non-associated alleles.[43 61] HLA-DRB1*01 genes alone are not associated with the severity of rheumatoid arthritis. However, when DRB1*04 genes are included in logistic regression analyses, they do not often

Table 5 Strength of the recommendations

Recommendations	No of studies evaluated	Level of evidence	Strength of recommendation
1 Early referral	35	Ib	B
2 Diagnosis of early synovitis	30	IIb	C
3 Minimum diagnostic procedure			D
4 Prediction of persistent and erosive arthritis	45	III	C
5 Early treatment start	27	Ia	A
6 Patient information	26	Ia/Ib	B
7 NSAIDs	11	Ia	B
8 Systemic and intra-articular glucocorticoids	21	Ia	A
9 Methotrexate is the anchor drug	24	Ia	A
10 Treatment strategies	22	Ib	B
11 Non-pharmaceutical interventions	32	Ia	B
12 Regular monitoring	11	Ia	A

NSAID, non-steroidal anti-inflammatory drug.

contribute to explaining variation in the model, which makes DRB1 genotyping a less suitable tool for prognostic purposes. The duration of cigarette smoking has also been shown to be an interesting susceptibility factor and a determinant of disease progression in rheumatoid arthritis, but this variable was not often investigated or selected as an independent variable in multivariate studies.

Abnormalities seen on MRI may be of prognostic interest.[40 41] In general, single variables have shown limited prognostic value, and several reports have tried to develop prediction models with a combination of the most reliable markers.[20 43 48 53] Though some of these models seem promising, the development and (cross)validation of a robust model, easy to use in all settings in clinical practice, is still pending.

Recommendation 5

Patients at risk of developing persistent and/or erosive arthritis should be started with DMARDs as early as possible even if they do not yet fulfil established classification criteria for inflammatory rheumatological diseases.

Four studies (category III) have shown that early arthritis is frequently undifferentiated at presentation,[65–68] and six studies (category III) have shown that classification criteria for established diseases have little discriminant value during the early months of the disease.[50 69–73] Recent studies have demonstrated that joint erosion occurs early in rheumatoid arthritis, and that more than 80% of patients with a disease duration of less than two years may already have radiographic evidence of joint damage. The concept of a "window of opportunity" for effective treatment of recent onset rheumatoid arthritis has been supported by one meta-analysis,[21] six RCTs,[22–25 74 75] and several comparative or observational studies.[11–13 26 76 77] Among patients with recent onset polyarthritis, those who received DMARD treatment early had a better outcome with regard to radiographic progression, function, and ability to work than those in whom DMARD treatment was delayed by a few months.[11–13 23 26 74] Results of a meta-analysis of 1435 patients also support this concept: disease duration at the time of DMARD initiation was shown to be the main predictor of the response to DMARD treatment.[21]

Recommendation 6

Patient information concerning the disease and its treatment and outcome is important. Education programmes aimed at coping with pain disability and the maintenance of work ability may be employed as adjunct interventions.

Provision of information should be an integral part of the management of any chronic disease. The expert committee considered that patient information concerning arthritis, its treatment, and its outcome was important. Three RCTs demonstrated that written information may increase knowledge about the disease.[78–80] One systematic review,[81] four RCTs,[82–85] and two controlled trials[86 87] showed that a self management education programme resulted in improved clinical outcome in rheumatoid arthritis, producing short term effects on disability, joint count, and patient global assessment, anxiety, and depression, but without any evidence of long term benefit.[81] There is only weak evidence that group education is better than individual education (category IV).[87 88]

In summary, patient information was considered important, and the benefits of educational interventions have been shown in clinical trials. In the opinion of the expert committee, however, it is difficult to prioritise a single educational intervention, because all interventions have only shown short term benefits, and are subjected to cross national and cultural variation. It is important to bear in mind that specific objectives in early arthritis have not been achieved, and that further evaluation is needed.

Recommendation 7

NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status.

Substantial evidence, including a Cochrane review in established rheumatoid arthritis but not in early (rheumatoid) arthritis, indicates that both classical and COX-2 selective, non-steroidal anti-inflammatory drugs (NSAIDs) are more effective than simple analgesics in relieving the signs and symptoms of active disease (category Ia).[89 90] Some data were missing to calculate the effect size of NSAIDs versus analgesics in rheumatoid arthritis.

However, there are concerns over the gastrointestinal, renal, and cardiovascular side effects of NSAIDs. Replacement of conventional NSAIDS by COX-2 selective drugs, or the addition of gastroprotective agents (misoprostol, double doses of H_2 blockers, and proton pump inhibitors) to classical NSAIDs can significantly reduce gastrointestinal complications such as the incidence of gastrointestinal bleeding (category Ia).[91] However, the long term use of COX-2 selective drugs has been associated with increased cardiovascular risk.[92 93] Probably, this increased cardiovascular risk is not limited to COX-2 selective drugs, but extends to all NSAIDs. Consequently, the US Food and Drug Administration and the European Medicines Agency have published recommendations for the use of these drugs. Among others, they recommend the shortest treatment duration possible and contraindications for at-risk patients. The expert committee felt there is no reason to assume that these observations should not be extrapolated to early arthritis. Symptomatic patients presenting with early arthritis should therefore be treated with NSAIDs after careful evaluation of gastrointestinal, renal, and cardiovascular status.

Recommendation 8

Systemic glucocorticoids reduce pain and swelling and should be considered as a (mainly temporary) adjunct to the DMARD strategy. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.

Several RCTs and three systematic reviews have shown that systemic low dose glucocorticoids, typically prednisone $\leqslant 10$ mg/day, were effective in relieving short term signs and symptoms in patients with rheumatoid arthritis.[94–99] Results of a recent open study of 100 patients with undifferentiated arthritis suggested that a single dose of intramuscular or intra-articular steroids may even induce remission,[100] although formal evidence for this strategy is lacking.

In addition, and despite controversial data, steroids are probably effective in slowing radiographic progression in early and established rheumatoid arthritis. In an RCT involving rheumatoid arthritis patients with a disease duration of less than two years, Kirwan[101] reported the superior efficacy of two years of continuous treatment with prednisolone, 7.5 mg daily, with respect to radiographic progression compared with standard care without prednisolone. In an RCT involving

patients with rheumatoid arthritis of less than one year duration, van Everdingen *et al*[102] compared treatment with prednisone 10 mg daily and NSAIDs. Only sulfasalazine was allowed in this study, but only after six months, and only as a rescue drug. The prednisone group showed significantly less radiographic progression at 12 and 24 months. The effect size of low dose steroids on the Larsen score compared with symptomatic treatments in these two studies was only 0.28 and 0.26, respectively, at 24 months. These data are supported by data from another RCT[103] and from two trials in early rheumatoid arthritis, which indicated that combination therapy including steroids was more effective in terms of radiographic progression than single DMARD therapy, but it is not possible to determine the specific benefits provided by steroid administration in these trials.[5 6 104] The published data have not all been positive. Paulus *et al*[105] were unable to show an effect of prednisone, $\leqslant$ 5 mg/day, in radiographic progression in a subgroup analysis of a three year RCT comparing etodolac and ibuprofen in 824 patients. A recent RCT by Capell *et al*[106] failed to demonstrate any significant difference in two year radiographic progression between prednisone, 7 mg/day, and placebo. In addition, subanalysis of two recent trials with new DMARDs did not show any added benefit of low dose prednisone with respect to radiographic progression.[4 107]

The positive short term effects of intra-articular corticosteroid administration in relieving local symptoms of inflammation in rheumatoid arthritis were shown in two RCTs.[108 109] Among the intra-articular corticosteroids, there is some indication that triamcinolone hexacetonide is the most effective.[110]

In summary, systemic glucocorticoids—either alone or as part of a DMARD combination strategy—are effective in the short term relief of signs and symptoms, and are probably effective in retarding radiographic progression in early and established rheumatoid arthritis. The systemic use of glucocorticoids in early arthritis has not yet been formally investigated. Preferably, treatment with glucocorticoids is temporary because of the risk of side effects—including weight gain, hypertension, diabetes, cataracts, and osteoporosis—which justify careful monitoring and appropriate prevention. Furthermore, the long term safety of low dose glucocorticoids is largely unknown. Intra-articular steroids may be effective as an adjunct to DMARDs in relieving local joint symptoms. There is still no evidence that intra-articular or intramuscular steroids alter the course of early arthritis.

Recommendation 9

Among the DMARDs, methotrexate is considered the anchor drug and should be used first in patients at risk of developing persistent disease.

At the root of this statement is the observation of a meta-analysis of patients with established rheumatoid arthritis, showing a significantly lower discontinuation rate of methotrexate as compared to other DMARDs (but leflunomide and tumour necrosis factor (TNF) blockers were not evaluated).[111] Several RCTs have proven the clinical efficacy of methotrexate. These RCTs were followed by observational studies clearly establishing that methotrexate is effective over long periods, and that it has a better toxicity profile than other DMARDs.[112–115] Importantly , methotrexate is one of the first conventional DMARDs with proven efficacy on radiographic progression in rheumatoid arthritis.[4] In early rheumatoid arthritis, two RCTs (of 12 and 18 months' duration) failed to demonstrate the superiority of methotrexate over other DMARDs such as sulfasalazine.[116 117]. However, recent RCTs with TNF blocking drugs have shown that methotrexate is almost as effective as TNF blocker monotherapy in patients with early (less than three years' duration) severe rheumatoid arthritis.[107 118]

An important argument for considering methotrexate as an anchor drug is that it can be combined with biological treatments if necessary. This has emerged from RCTs showing greater efficacy for the combination of TNF blocking drugs with methotrexate than for monotherapy.[9 118–120] The combination of methotrexate with TNF blockers appears to convey the maximum therapeutic effect currently obtainable, both in established and early rheumatoid arthritis. The combination of methotrexate with sulfasalazine has not been shown to be superior to single drug treatment.[116–117] Despite interesting reports,[5 7 104 121–128] whether the combination of methotrexate with other DMARDs is more efficient than monotherapy needs further investigation.

Leflunomide, and to a lesser extent sulfasalazine, have a similar clinical efficacy to methotrexate in established and recent rheumatoid arthritis (category Ia).[124] Leflunomide is as effective as methotrexate in slowing radiographic damage.[4] Sulfasalazine, in contrast, may be inferior to leflunomide and methotrexate in the long term.

In summary, methotrexate appears to be an anchor drug in rheumatoid arthritis, both as monotherapy and in combination with conventional DMARDs or TNF blocking drugs for most patients with rheumatoid arthritis.

Although formal evidence that prioritises methotrexate as the first DMARD in early arthritis or early rheumatoid arthritis is lacking, the expert committee recommends that treatment should be started with methotrexate (unless contraindicated) in patients at risk of persistent or erosive disease. This recommendation is based on its clinical and radiological efficacy in combination with the relatively beneficial safety profile, and on its beneficial properties in treatment combinations. Leflunomide, and to a lesser extent, sulfasalazine are considered the best alternatives.

Recommendation 10

The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies (DMARDs including biological agents)

The introduction of new drugs that can control disease progression, and the demonstration that DMARDs are more effective if used early rather than later in disease progression, have led to crucial changes in management goals in early arthritis and early rheumatoid arthritis. The objective should now be to achieve remission in order to prevent structural damage and long term disability.

One recent therapeutic strategy in the treatment of rheumatoid arthritis is the early use of combination therapy with conventional DMARDs ("intensive" therapy). Some RCTs have evaluated the combination of two DMARDs (mainly methotrexate-sulfasalazine or methotrexate-ciclosporine) in early rheumatoid arthritis, with controversial results both for clinical efficacy and for radiographic evidence of progression.[116 117 121 123 125 126] However, a combination of methotrexate and sulfasalazine with high dose steroids in a step-down therapeutic strategy (COBRA) resulted in protracted effects on radiographic progression, compared with sulfasalazine monotherapy in 155 patients with early rheumatoid arthritis (category 1b).[5 104] These results are consistent with those from the FIN-RACo study, in which 197 patients with onset of rheumatoid arthritis within the previous two years were randomly assigned to receive either a four-drug regimen, with methotrexate, sulfasalazine, hydroxychloroquine, and

prednisolone (5 mg/d), or a single DMARD.[6 127 128] After 18 months, a greater proportion of the combination therapy group were in remission. After five years, the combination group were less likely to have radiographic progression, and the work disability rate was lower compared with the patients on monotherapy. However, in neither study was there an arm with DMARD monotherapy plus steroids.

The concept that intensive interventions early in the course of persistent arthritis may profoundly affect long term radiographic progression is also supported by four recent RCTs with TNF blockers in early rheumatoid arthritis. In patients with a disease duration of less than three years, the use of a TNF blocking drug (adalimumab, etanercept, or infliximab)—especially in combination with methotrexate—revealed an increased rate of clinical remission and slowing of radiographic progression compared with methotrexate monotherapy.[118–120 129] The effect size of such a combination versus methotrexate alone on total radiographic score in patients with early rheumatoid arthritis varied from 0.42 to 0.96. These data are consistent with those from several RCTs in established rheumatoid arthritis, showing that intensive treatment with a combination of conventional DMARDs plus steroids or with biological therapy in combination with methotrexate may provide superior clinical and radiological efficacy than monotherapy.[8–10]

In addition, a recent RCT compared four treatment strategies in early rheumatoid arthritis, including a progressive step-up regimen, sequential monotherapy, a triple step-down strategy with methotrexate, sulfasalazine, and high dose prednisone, and infliximab plus methotrexate.[7] The two groups with initial intensive treatment (combination and infliximab group) showed a more rapid clinical response and a better radiographic outcome than the sequential monotherapy or the step-up DMARD therapy groups.

In the TICORA study,[14] patients with early rheumatoid arthritis were randomly assigned to an intensive treatment in order to reach a low disease activity state (DAS44 <2.4) close to remission, or to regular clinical care The intensive treatment group developed less radiographic damage than the control group after 18 months of follow up, suggesting an association between remission (or low disease activity) and further joint destruction (category Ib). Other data support the need to achieve clinical remission in order to control the disease process, including the long term follow up of two Dutch cohorts which found a positive relation between disease activity score (DAS) and 28 joint disease activity score (DAS28) and radiological progression, after adjustment for time effects and baseline predictors of radiological destruction and their interactions with time[130] (category III). In the PREMIER study,[118] the ASPIRE study,[119] and the TEMPO study (despite the fact that it was done in established rheumatoid arthritis),[9 131] clinical remission was achieved in some patients and higher remission rates were associated with arrest of radiographic progression (maybe even repair) and better physical function.

In summary, initial intensive treatment provides a better outcome than DMARD monotherapy including methotrexate in patients with recent onset chronic arthritis, but mainly in a subset of patients with severe disease.[119] Consequently, regarding the benefit to risk ratio and the cost-effectiveness of these strategies, a reasonable course of action should be initial DMARD monotherapy with methotrexate (or leflunomide or sulfasalazine). However, the expert committee felt that there is ample evidence that with modern treatment combinations with or without biological agents clinical remission is an achievable goal. There is also indirect evidence from various RCTs and observational studies that remission is associated with better radiographic outcome and better preservation of physical function. As there is emerging evidence that maintaining remission is as important as achieving remission, it is obvious that disease activity should be closely monitored in order to change DMARD therapy and strategy if necessary (''benchmarking''). The first studies supporting this view have just been published.[14]

Recommendation 11

Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as treatment adjunct to pharmaceutical interventions in patients with early arthritis.

The effect of non-pharmaceutical treatments has not been investigated in early arthritis and can only be extrapolated from the results of several RCTs and eight Cochrane reviews in established rheumatoid arthritis. RCTs have shown that joint specific dynamic exercises may improve strength and physical function in rheumatoid arthritis, but without a clear effect on pain or disease activity.[132 133] However, the optimal exercise programme has not yet been determined. One recent RCT and a Cochrane review reported a positive effect of occupational therapy on functional ability and self management, but without an effect on disease activity.[134 135] Hydrotherapy in rheumatoid arthritis has been evaluated in two recent meta-analyses,[136 137] with positive findings but insufficient evidence to support a strong recommendation.

Nine RCTs have been undertaken to investigate the efficacy of diets. The results are controversial—the diets and the study designs varied widely, and most of the trials with diets only included highly selected and motivated patients. A one year study randomised 66 patients to receive a vegetarian diet free of gluten or a well balanced non-vegan diet. The vegetarian diet group experienced significantly better effects in most of clinical variables, including the ACR 20 response, as compared with the non-vegetarian group.[138] Two other RCTs found a positive effect of a vegetarian diet on pain and indices of disease activity.[139 140] Numerous other non-pharmaceutical interventions have been investigated in patients with rheumatoid arthritis. Acupuncture, laser therapy, use of compression gloves, transcutaneous electrical nerve stimulation (TENS), ultrasound, thermotherapy, use of splints or ortheses, and homoeopathy are examples of non-pharmaceutical interventions with which controversial effects have been reported in RCTs.[141–144] When positive, the RCTs showed short term relief of pain only, rather than an effect on disease activity.

In summary, some non-pharmaceutical interventions—such as dynamic exercises, occupational therapy and hydrotherapy—have shown indisputable, often symptom relieving effects in established rheumatoid arthritis. There is limited evidence that a vegetarian diet may have a modest effect on symptoms. The efficacy of non-pharmaceutical interventions in early arthritis has not been formally tested, and there is no indication that they improve long term outcomes such as radiographic progression. The expert committee therefore felt that non-pharmaceutical interventions should only be applied as an adjunct to pharmaceutical treatment in patients with early arthritis.

Recommendation 12

Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessments, ESR, and CRP. Arthritis activity should be assessed at one to three month intervals, for as long as remission is not achieved. Structural damage should be assessed by *x* rays

Table 6 Research agenda based on expert opinion

- Ultrasonography and power Doppler should be validated for the diagnosis of early synovitis
- MRI should be validated for the diagnosis of synovitis, for showing early erosions and for the prognosis of further joint destruction.
- Accurate classification and diagnostic criteria for early (rheumatoid) arthritis are still lacking and need to be developed.
- Available prediction algorithms for persistent and/or erosive arthritis, and for long term disability should be further evaluated.
- Randomised controlled trials of non-pharmacological interventions in early arthritis are needed.
- The most efficient and effective information/education interventions and exercise programmes for early arthritis need to be determined.
- The role of glucocorticoids in very early arthritis should be evaluated.
- Whether the temporary use of glucocorticoids can prevent the progression of joint destruction if started in early arthritis should be further investigated.
- Effects of temporary use of intensive treatments, such as biologic agents in early arthritis, should be investigated to test if prevention of erosions and cure (a long term remission) of the disease is possible.
- Therapeutic strategies in early arthritis should be tested on the basis of prediction models.
- Studies with an appropriate design to determine the comparative effectiveness and cost-effectiveness of different therapeutic strategies are required.

every 6 to 12 months during the first few years. Functional assessment (for example, HAQ) can be used to complement the disease activity and structural damage monitoring.

This statement is supported by at least three RCTs.[7 14 145] In the TICORA study, patients with recent onset rheumatoid arthritis were randomly assigned to receive routine DMARD treatment at the discretion of the treating rheumatologist, or intensive treatment with monthly assessment of clinical disease activity.[14] In this latter group, the treatment was intensified or drug combinations were used if the effect on disease activity was insufficient, as defined by a DAS44 <2.4. This intensive strategy appeared to be significantly more effective at all follow up visits throughout the first 18 months, in terms of both clinical symptoms and radiographic progression.

Intensive care based on regular monitoring of DAS28 or DAS44 was associated with better outcome in two recent trials,[7 145] and other validated composite indices can be used to monitor disease activity equally reliably.[146] No evidence from an appropriately designed clinical trial exists to support monitoring of radiographic progression. The expert committee considered monitoring of radiographic progression useful in view of the objective of the management of early arthritis (to prevent joint destruction), the observation that radiographic progression is greatest during the first two years after disease onset, and the appreciation that radiographic progression is clinically meaningful in case of a change of 4 Sharp units (during six months follow up) and can be reliably established at the group level after a three to six months interval[147] (category III). In order to facilitate radiographic monitoring, it could be desirable to use the simple erosion and narrowing score (SENS), a scoring method based on the van der Heijde modified Sharp score and validated for use in clinical practice.[148]

DISCUSSION

These 12 recommendations, presented in short sentences, are based on recent research evidence up to January 2005 and on expert opinion. The task force has followed the EULAR standardised operating procedures for formulating recommendations.[15] Similar methods have been also used to develop the EULAR recommendations for the management of knee and hip osteoarthritis.[149 150] Early arthritis is frequently undifferentiated, and the major issues of interest are diagnosis, prognosis, and treatment. As these issues cannot be considered independently, the expert committee has decided to focus its work on "early undifferentiated arthritis with a certain propensity to become persistent and erosive", and to use an operational definition for "management" that covers the entire process, including referral, diagnosis, prognosis, and treatment. As a result, these recommendations are not aimed only at rheumatologists but also at GPs and potentially at medical students. Types of arthritis that do not fit the framework outlined above were excluded in this exercise.

As mentioned already by others,[149] the expert committee did not find it helpful to score the quality of the studies, both because the topics that were examined varied widely and because of the heterogeneity of the studies that were found The committee chose to grade the level of evidence provided by every study, which was based on the methodology of the study, and took this grading into consideration when discussing the content and the strength of the recommendations. An important consideration in the discussions always was whether the type of study fitted the content of the research question that was at the basis of the literature search. Besides evidence obtained from published reports, expert opinion and the clinical experience of the expert committee turned out to be very important for reaching consensus, and for formulating and weighing the strength of the recommendations. The expert committee had to face an important limitation in that most of the published data from which the recommendations were derived were based on studies in patients with early rheumatoid arthritis or established rheumatoid arthritis, rather than on studies in early arthritis. Nevertheless, the expert committee considered the data in early rheumatoid arthritis robust enough and relevant enough to be extrapolated to "early arthritis with a certain propensity to become persistent and/or erosive". By doing so, the expert committee has implicitly subordinated the classification of rheumatoid arthritis to a clinical diagnosis of potentially persistent erosive arthritis, which can be interpreted as a novelty. This new line of thinking enabled the task force to highlight key points in the management of early arthritis, including the need for early referral to a rheumatologist; the prediction of persistent and erosive disease; the requirement for an early start of efficient DMARD treatment in all patients at risk of developing persistent or erosive arthritis; the key role of methotrexate as the first and anchor drug; the objective of the therapeutic strategy in inducing remission and preventing joint destruction; and the need for regular monitoring to adapt the strategy as necessary and detect adverse events.

Reviewing the literature, the committee felt that there was a need to develop new tools for early and accurate diagnosis and prognosis. These include new imaging and serological measures

and also prediction algorithms for long term outcome. Also lacking is information about the effectiveness of non-pharmacological interventions, the role of glucocorticoids, and the comparative effectiveness and cost-effectiveness of different strategic modes in early arthritis. The task force proposed 11 items considered the most important for future research according to current available evidence (table 6).

New effective treatments for rheumatoid arthritis and new strategic concepts in the treatment of the disease have definitely changed thinking about the management of early arthritis.

The current EULAR recommendations on the management of early arthritis value the recent therapeutic developments, but they also point to the variety of available treatment, and the heterogeneity of patients in whom these treatment should be applied. Management according to protocols will become increasingly difficult, and every health professional should choose the most appropriate management strategy for every individual patient. The recommendations should be considered a reflection of current thinking in the field of early arthritis, supported by firm evidence if possible, and dressed up by expert opinion if necessary, in order to serve as an aid for health professionals and patients who have to make decisions about the most appropriate individual management strategy. To that end, it is hoped that the recommendations will be widely disseminated and discussed within the rheumatological community and other physicians taking care of patients with early arthritis, and that they will help improve the standard of care for patients with arthritis across different health care systems. Obviously these recommendations will need an update after few years, in order to incorporate new scientific evidence.

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EXTENDED REPORT

EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT)

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Objectives: To update the EULAR recommendations for management of knee osteoarthritis (OA) by an evidence based medicine and expert opinion approach.

Methods: The literature search and guidelines were restricted to treatments for knee OA pertaining to clinical and/or radiological OA of any compartment of the knee. Papers for combined treatment of knee and other types of OA were excluded. Medline and Embase were searched using a combination of subject headings and key words. Searches for those treatments previously investigated were conducted for January 1999 to February 2002 and for those treatments not previously investigated for 1966 to February 2002. The level of evidence found for each treatment was documented. Quality scores were determined for each paper, an effect size comparing the treatment with placebo was calculated, where possible, and a toxicity profile was determined for each treatment modality.

Results: 497 new publications were identified by the search. Of these, 103 were intervention trials and included in the overall analysis, and 33 treatment modalities were identified. Previously identified publications which were not exclusively knee OA in the initial analysis were rejected. In total, 545 publications were included. Based on the results of the literature search and expert opinion, 10 recommendations for the treatment of knee OA were devised using a five stage Delphi technique. Based on expert opinion, a further set of 10 items was identified by a five stage Delphi technique as important for future research.

Conclusion: The updated recommendations support some of the previous propositions published in 2000 but also include modified statements and new propositions. Although a large number of treatment options for knee OA exist, the evidence based format of the EULAR Recommendations continues to identify key clinical questions that currently are unanswered.

Osteoarthritis (OA) is the most common form of arthritis in Western populations. It is characterised pathologically by both focal loss of articular cartilage and marginal and central new bone formation. OA of the knee, the principal large joint to be affected, results in disabling knee symptoms in an estimated 10% of people older than 55 years, a quarter of whom are severely disabled.[1] The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater than that due to any other medical disorder in the elderly.[2] A recent World Health Organisation report on the global burden of disease indicates that knee OA is likely to become the fourth most important global cause of disability in women and the eighth most important in men.[3] The annual costs attributable to knee OA are immense. There is therefore a burden on health from both morbidity and cost. Radiographic evidence of knee OA in men and women aged over 65 is reported in 30% of subjects,[4] around one third of whom are symptomatic. Annual arthroplasty rates in Europeans over the age of 65 vary from country to country but are of the order of 0.5–0.7 per 1000.[5]

The aetiology of knee OA is multifactorial and includes both generalised constitutional factors (for example, aging, sex, obesity, heredity, reproductive variables) and local adverse mechanical factors (for example, trauma, occupational and recreational usage, alignment).[6 7] There is a significant genetic component to the prevalence of knee OA, with heritability estimates from twin studies of 0.39–0.65 independent of known environmental or demographic confounders.[8]

Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity and mortality. Current treatments aim at alleviating these symptoms by several different methods:

- Non-pharmacological treatments (for example, education, exercise, lifestyle changes)
- Pharmacological treatments (for example, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), topical treatments)

Abbreviations: ES, effect size; HA, hyaluronic acid; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; QS, quality score; RCT, randomised controlled trial; TKR, total knee replacement

- Invasive interventions (for example, intra-articular injections, lavage, arthroplasty).

The objectives of management are to:

- Educate the patient about OA and its management
- Alleviate pain
- Improve function and decrease disability
- Prevent or retard progression of the disease and its consequences.

Current evidence to support the various treatments in current use, however, is very variable.

Guidelines on the management of knee and hip OA have been published by the Royal College of Physicians[9] and the American College of Rheumatology.[10] In 1998, EULAR commissioned a steering group to review the evidence for the treatment of knee OA. Recommendations for treatment were developed as a result of this evidence based review and presented in 2000.[11] These guidelines, however, were restricted to a limited number of treatment modalities and only reviewed evidence up until December 1998. We therefore have updated the recommendations by extending the literature search to February 2002 and by including all treatments used in knee OA.

METHODS

Membership of guidelines steering group committee

The members of the expert committee on knee OA reconvened in November 2001 to establish the methodology in updating the evidence base and recommendations for the treatment of knee OA. The initiative, endorsed by ESCISIT, involved a committee of experts in OA (19 rheumatologists, four orthopaedic surgeons) and one research fellow from 13 European countries.

The aims of the committee were:

- To describe all the therapeutic modalities used in the treatment of knee OA and to review the current level of evidence attributable to each of these treatments
- To produce a list of 10 recommendations for the management of knee OA and to examine the degree to which these recommendations are supported both by research evidence and the consensus of expert opinion
- To specify 10 recommendations for the future research agenda for the management of knee OA.

Evidence based review

Search strategy

To maintain continuity from the previous search, Medline OVID and BIDS Embase were the databases searched systematically. The searches for those treatment modalities previously investigated were conducted for the period January 1999 to February 2002 and for those modalities not previously investigated from 1966 to February 2002. In the search strategy, all English and other European language publications in the form of systematic reviews, meta-analyses, randomised controlled trials (RCTs), controlled trials, and observational studies were included. Publications in non-European languages were excluded.

Selection of manuscripts

All trials that assessed the effects of a treatment for knee OA on pain and/or function were included. Thirty three such individual treatment modalities were identified; NSAIDs are divided into two subsets, conventional (non-selective) NSAIDs and COX 2 selective NSAIDs (coxibs), but overall recognised as one group (table 1). For the purpose of the review knee OA was defined as patients with clinical and/or radiological evidence of knee OA. Only papers exclusively studying knee OA were included at all stages of the analysis; those combining hip and knee OA were excluded. The previous literature search included papers combining hip and knee OA in its qualitative data; these were reviewed and if the results for hip and knee OA could not be separated from one another, the publication was rejected.

Quality scoring of manuscripts

The methodological design of each study was scored according to a predetermined proforma.[12] This methodological checklist provided a quality assessment of the information provided by each individual publication, particularly addressing study design and methodology and the statistical power of each study. Studies were scored 0–1 for 26 questions and 0–2 for one question, giving a maximum total of 28. Power calculations were scored as 1 if present and 0 if absent. If probability values were reported in the results, a score of 1 was given and 0 if absent. A single assessor scored English language publications and a second assessor validated these scores in a blinded fashion. Non-English European language publications were assessed by individual members of the EULAR steering group committee fluent in the language of the publication. All quality scores were collected and recorded centrally.

Estimation of a treatment effect size

Quantitative analysis of treatment effect was assessed, where possible, by calculating the effect size (ES) for validated outcome measures of pain and function. A software package was used for this purpose.[13] An ES is the standardised mean difference between a treatment group and a control group for an outcome variable[14]—in this case, pain and function. It reflects the magnitude of difference between two groups in standardised terms and is free of units. The mean and distribution of values for the baseline placebo and active treatment, and end point placebo and active treatment, and difference from baseline to end point were tabulated for each of the outcome measures recorded.

The ES and data displayed in this paper in all cases are calculated against placebo. Clinically, an ES of 0.2 is considered small, 0.5 is moderate (and would be recognised clinically), and greater then 0.8 is large. All data were collected and recorded centrally.

Categorising evidence

Categories of evidence were adapted from the classification of the United States Agency for Health Care Policy and Research. Evidence was categorised according to study design reflecting susceptibility to bias. Table 2 shows the categories in descending order of importance. Questions posed by the recommendations were answered using the best evidence available. If, for example, a question could be answered by category 1 evidence then weaker design publications were not reviewed.

Strength of recommendation

The strength of recommendation for an intervention was graded A-D (table 3) by members of the editing subcommittee of the task force, after examination of the evidence in detail. The strength of recommendations is based not only on the level of evidence but also upon consideration of the following: the ES of the intervention; the side effect profile; the applicability of the evidence to the population of interest; practicality of delivery; and economic considerations. In this way the different treatments could be scored in a pragmatic manner more applicable to everyday clinical practice.

Assessment by expert panel opinion

Experts' opinion approach

After informing the expert committee about the results of the literature search and the level of evidence found for each treatment modality, two sets of 10 recommendations were

Table 1 Treatment modalities identified for the treatment of knee OA

Non-pharmacological	Pharmacological	Intra-articular	Surgical
Education	Paracetamol	Corticosteroid	Arthroscopy
Exercise	NSAIDs	Hyaluronic acid	Osteotomy
Insoles	Opioid analgesics	Tidal irrigation	UKR
Orthotic devices	Sex hormones		TKR
Weight loss	SYSADOA		
Laser	Psychotropic drugs		
Spa	Topical NSAID		
Telephone	Topical capsaicin		
Vitamins/minerals			
Pulsed EMF			
Ultrasound			
TENS			
Acupuncture			
Nutrients			
Herbal remedies			

EMF, electromagnetic field therapy; TENS, transcutaneous electrical nerve stimulation; NSAIDs, non-steroidal anti-inflammatory drugs; SYSADOA, **SY**mptomatic **S**low **A**cting **D**rugs for **OA** (includes avocado/soybean unsaponifiables (ASU), chondroitin, diacerein and glucosamine); UKR, unicompartmental knee replacement; TKR, total knee replacement.

proposed following a five stage Delphi technique:(*a*) the final expert evidence and opinion based recommendations for treatment, and (*b*) recommendations for future research agendas.

Toxicity profile

Once the definitive list of the treatments and their level of evidence was communicated, the committee ranked the potential toxicity of each intervention. This was expressed as a 100 mm visual analogue scale, in which 0 was "not toxic at all" and 100 was "very toxic". Figure 1 shows the results obtained.

It was felt by members of the panel after the initial opinion had been sought that the NSAID group should be subdivided into conventional NSAIDs and coxibs. This was therefore performed at a later meeting.

Level of evidence of the experts' opinion approach

The researchers who undertook the literature search evaluated the level of evidence in order to answer the questions posed by the 10 recommendations for management of knee OA as proposed by the panel.

RESULTS

Evidence based approach

497 new publications were identified by the search strategy. Of these, 103 were intervention trials and therefore included in the overall analysis; 99 of these were intervention trials using at least one of the 33 treatment modalities identified, 3 were systematic reviews, and 1 was a meta-analysis. The previously identified publications were also reviewed and those that were not exclusively knee OA in the initial analysis were rejected. In total, 545 publications were included. Treatments that are no longer in use (for example, glycosaminoglycan polyscaccharides) were not included in the tabular analysis. Table 4 outlines the different treatment modalities with quality scores and effect sizes where they could be calculated. Table 5 outlines the level of evidence for each and also the strength of recommendation from the expert panel.

A large number of trials examined NSAIDs. 135 NSAID trials were included in this analysis, but only 35 of these had a placebo arm and the ES could only be calculated in five of these. Median quality scores were much higher for the newer coxib trials than for trials investigating conventional NSAIDs.

Quality scores varied enormously for many of the interventions. Those studies conducted more recently tended to be of a higher design quality. Median quality scores were highest for glucosamine and chondroitin sulphate trials and lowest for the surgical trials, tending to parallel the level of evidence found for each modality.

Of the 33 treatment modalities, 29 were supported by evidence from at least one RCT and were graded as either 1A or 1B for category of evidence. Of the surgical trials, only those assessing arthroscopy ± debridement were supported by evidence from RCTs.

Table 2 Categories of evidence

Category	Evidence from:
1A	Meta-analysis of RCTs
1B	At least one RCT
2A	At least one controlled study without randomisation
2B	At least one quasi-experimental study
3	Descriptive studies, such as comparative, correlation or case-control studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities

Toxicity profile

NSAIDs, opioid analgesics, and psychotropic antidepressant drugs were regarded as having a similar toxicity profile in long term use to that of joint replacement surgery.

When NSAIDs were subdivided into conventional and coxib groups, the results showed that the perceived mean toxicity of non-selective NSAIDs was 51 mm and the coxib mean 41 mm on a 100 mm visual analogue scale.

Experts' opinion approach

Tables 6 and 7 summarise the final recommendations for management and future research agenda as proposed by the expert committee.

Table 3 Strength of recommendation

Category	Directly based on:
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendation from category 1 evidence
C	Category 3 evidence or extrapolated recommendation from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendation from category 2 or 3 evidence

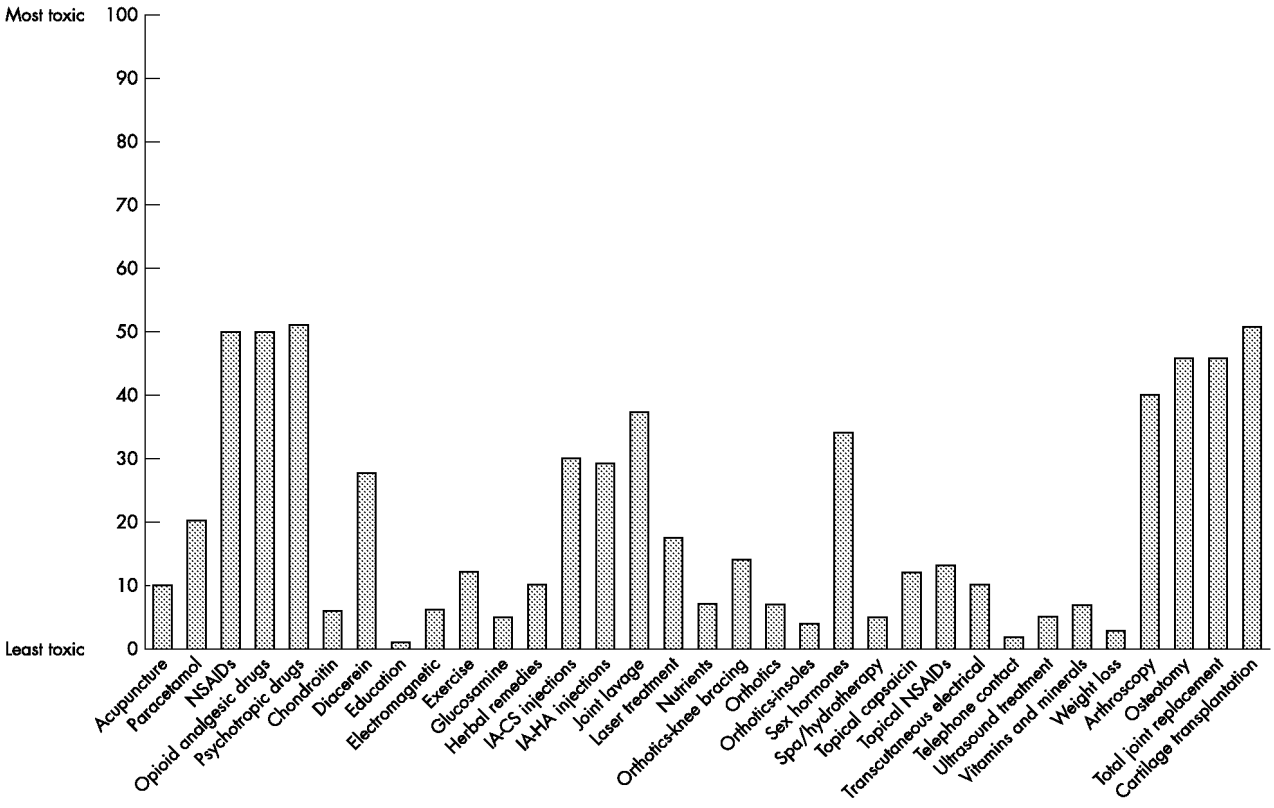

Figure 1 Toxicity profile of the treatment modalities based on expert opinion (23 experts).

Assessment of the propositions

The propositions are ranked in order of importance as debated by the expert opinion panel.

1. The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities

Although this statement is logical and represents common clinical practice, there is little direct evidence from appropriately designed factorial RCTs to support this statement. There is, however, a wealth of indirect evidence from RCTs in which all subjects were receiving analgesics or NSAIDs at baseline that non-pharmacological treatments offer additional benefit over and above analgesic or NSAID usage. These have demonstrated that exercise programmes[15](quality score (QS) 26), physiotherapy[16] (QS 26), weight loss combined with exercise[17](QS 21), education[18] (QS 12), and wedged insoles[19 20](QS 10, 11) offer additional benefit when used with an analgesic or NSAID regimen. There is therefore a reasonable evidence base to support this statement (1B).

2. The treatment of knee OA should be tailored according to:

- Knee risk factors (obesity, adverse mechanical factors, physical activity)
- General risk factors (age, comorbidity, polypharmacy)
- Level of pain intensity and disability
- Sign of inflammation—for example, effusion
- Location and degree of structural damage.

This statement represents ideal practice and includes clinical markers that are often used to guide clinical decisions. Clinical trials predominantly investigate the efficacy of one or two specific monotherapies in highly selected homogeneous populations of otherwise fit subjects with knee OA. These data therefore are not directly applicable to the whole population of subjects with OA. Those studies that have examined the predictors of response to treatment often have limited statistical power, and therefore results are often inconclusive. An example is the presence of an effusion predicting a response to intra-articular steroids where two studies have shown conflicting results[21 22](QS 22, 17). One RCT involving 84 patients confirmed short term symptom benefit of steroid over placebo and found a better outcome in those with an effusion. However, a randomised crossover study of methylprednisolone versus saline found no clinical predictors of response, suggesting that steroid injection should not be reserved just for those with effusion alone.

As well as the expected relative benefits, potential dangers and costs of the intervention must clearly be taken into account. This has relevance to both medical and surgical interventions. The holistic approach to the patient is universally accepted: it has obvious validity but no research based justification specific to knee OA.

3. Non-pharmacological treatment of knee OA should include, education, exercise, appliances (sticks, insoles, knee bracing) and weight reduction

Education and provision of information should form an integral part of the management of any chronic disease. This is a professional obligation and should include details of the disease, its investigations, and management. Practitioners should tailor any treatment to the individual needs of the patient and this concept can be discussed within education. Several large RCTs and a meta-analysis have demonstrated the benefits of different educational techniques in reducing pain and increasing coping skills, but with little impact on function in patients with knee OA.[23] Education has also been shown to result in fewer visits to

Table 4 Summary of the effect size versus placebo, quality scores, and number of studies identified

Intervention	Number of studies	Positive to placebo	Quality score (range)	Quality score (median)	Effect size versus placebo
Acetaminophen/paracetamol	5	1/1	17–26	20	
Opioid analgesic/other	6	2/3	11–24	19	
NSAID					
Conventional NSAID	130	27/31	5–27	17	0.47, 0.50, 0.76, 0.96,
Coxibs	5	4/4	18–25	23	0.50
Antidepressant	1	1/0	16	–	
Topical NSAID	9	5/7	18–26	22	−0.05, 0.16, 0.31, 0.91, 1.03
Topical capsaicin	2	2/2	21, 26		0.41, 0.56
Sex hormones	2	0/1	15, 20		
SYSADOA					
Glucosamine	8	4/6	14–27	24	0.43, 0.53, 1.02
Chondroitin	5	5/5	20–27	24	1.23, 1.37, 1.44, 1.50
Diacerein	1	1/1	22	22	
ASU	3	3/3	21–24	23	0.32, 1.72
Nutrients	2	2/2	4,25	–	0.65
Herbal remedies	5	3/3	14–27	20	0.23, 1.32
Minerals/vitamins	1	0/1	24	24	
Education	7	3/3	11–15	13	0.28, 0.35
Exercise	40	8/9	5–26	15	0.57, 0.59, 1.0
Telephone	3	1/1	16–18	18	1.09
Acupuncture	6	2/2	11–22	16	0.25, 1.74
Laser	2	1/1	12,17		0.87
Pulsed EMF	2	2/2	18,19		
Spa	5	3/3	12–17	15	1.0
TENS	7	6/6	12–22	17	0.76
Ultrasound	1	0/1	20		
Weight loss	2	1/1	11,15		
Insoles	5	0/1	3–15	11	
Orthotic device (knee brace/ patella tape/elastic bandage	9	3/3	7–20	15	
IA Hyaluronic acid	35	18/20	9–26	20	0.0, 0.04, 0.48, 0.49, 0.88, 0.9
IA Corticosteroid	9	6/7	4–22	16	1.27
Lavage/tidal irrigation	7	1/1	11–25	18	0.84
Arthroscopy	14	–	6–17	10	
Osteotomy	26	–	5–15	11	
Unicompartmental knee replacement	15	–	4–16	11	
Total knee replacement	35	–	4–23	13	

primary care and therefore also has a cost implication. In a study of 211 patients with knee OA, 80% of the costs of delivering effective self care education were offset within a year by the reduced frequency and costs of primary care visits.[24] Education techniques shown to be effective include individualised education packages[25] (QS 12), regular telephone calls[26] (QS 17), group education[27](QS 20), patient coping skills[28] (QS 13), and spouse assisted coping skills training[29] (QS 15).

There is evidence from large RCTs that joint-specific exercises reduce pain and improve function in patients with knee OA. However, the optimal exercise regimen has not yet been determined. Exercise can be divided into joint-specific strength and range of motion exercises and general aerobic conditioning and can be either directly supervised on land or water or offered as a home based, self directed programme. A two centre RCT of 439 older patients with knee OA demonstrated that the cumulative incidence of disability for activities of daily living was lower in both exercise groups (aerobic exercise and resistance exercise) than in a no-exercise control group[30](QS 24). The effectiveness of home exercise on knee OA has been explored in several RCTs, showing reduced pain scores and improved function[15 31 32] (QS 26, 26, 20). Aerobic and isokinetic exercise regimens have also been effective in improving function and gait, and decreasing pain[16 27 33 34] (QS 26, 20, 19, 25). No differences were found between a land based exercise programme and an aquatic programme, although both showed significant improvements in pain and function[35](QS 17). Importantly, some of these studies report long term improvements (6–18 months). ES for exercise ranged from 0.57 to 1.0.

One RCT in 119 patients demonstrated that the pain and function of patients with varus knee OA using a knee brace improved significantly compared with those who did not use a brace[36](QS 20). An RCT comparing laterally wedged insoles with neutrally wedged insoles showed no statistical difference between the two groups. However, the group using laterally wedged insoles had a greater reduction in NSAID use together with increased compliance[37](QS 25). Two controlled studies of insoles[19 20] (QS 10, 11) demonstrated an improvement over an analgesic control group. A study of cross over within subjects suggested that the pain relief and improvement in function reported might be due in part to the reduced external varus moment and medial compartment load short term[38](QS15). No RCTs have examined walking sticks or elastic bandage in the management of knee OA. Application of an elastic bandage in 68 patients reduced knee pain significantly in a short term study of cross over within subjects [39](QS 20).

Although recommended to virtually all patients with knee OA, the relationship between weight reduction and knee OA has only been assessed formally in two studies. A large cohort study[40] (QS 15) showed that weight loss reduced the risk of

Table 5 Level of evidence based on the literature search, and strength of recommendation based on both evidence and expert opinion

Intervention	Level of evidence	Effect size Range	Strength of recommendation
Acetaminophen/paracetamol	1B		A
Opioid analgesics	1B		B
NSAIDs			
Conventional NSAID	1A	0.47–0.96	A
Coxibs	1B	0.5	A
Antidepressant	1B		B
Topical NSAID	1A	−0.05–1.03	A
Topical capsaicin	1A	0.41–0.56	A
Sex hormones	2B		C
SYSADOA			
Glucosamine	1A	0.43–1.02	A
Chondroitin	1A	1.23–1.50	A
Diacerein	1B		B
ASU	1B	0.32–1.72	B
Nutrients	1B	0.65	B
Herbal remedies	1B	0.23–1.32	B
Minerals/vitamins	1B		C
Education	1A	0.28–0.35	A
Exercise	1B	0.57–1.0	A
Telephone	1B	1.09	B
Acupuncture	1B	0.25–1.74	B
Laser	1B	0.87	B
Pulsed EMF	1B		B
Spa therapy	1B	1.0	C
TENS	1B	0.76	B
Ultrasound	1B		C
Weight loss	1B		B
Insoles	1B		B
Orthotic device (knee brace/ patella tape/elastic bandage	1B		B
IA Hyaluronic acid	1B	0.0–0.9	B
IA Corticosteroid	1B	1.27	A
Lavage/tidal irrigation	1B	0.84	B
Arthroscopy ± debridement	1B		C
Osteotomy	3		C
UCKR	3		C
TKR	3		C

developing symptomatic knee OA in women. A more recent RCT demonstrated that weight loss combined with exercise reduces pain and improves function in older adults for at least six months; unfortunately, no group had weight loss alone[17](QS 21).

In summary, there is good evidence that education (1A) and exercise regimens (1B) reduce pain in knee OA and that exercise regimens also improve function. The use of appliances and weight loss seem sensible options in patients with knee OA, but are only supported by relatively weak evidence, with the exception of knee bracing which has level (1B) evidence for reduction in pain and improvement in function.

4. Paracetamol is the oral analgesic to try first and, if successful, the preferred long term oral analgesic

Paracetamol is frequently used as self medication for the treatment of mild to moderate pain. It is the recommended

Table 6 Final set of 10 recommendations based on both evidence and expert opinion

1	The optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities
2	The treatment of knee OA should be tailored according to: (a) Knee risk factors (obesity, adverse mechanical factors, physical activity) (b) General risk factors (age, comorbidity, polypharmacy) (c) Level of pain intensity and disability (d) Sign of inflammation—for example, effusion (e) Location and degree of structural damage
3	Non-pharmacological treatment of knee OA should include regular education, exercise, appliances (sticks, insoles, knee bracing), and weight reduction
4	Paracetamol is the oral analgesic to try first and, if successful, the preferred long term oral analgesic
5	Topical applications (NSAID, capsaicin) have clinical efficacy and are safe
6	NSAIDs should be considered in patients unresponsive to paracetamol. In patients with an increased gastrointestinal risk, non-selective NSAIDs and effective gastroprotective agents, or selective COX 2 inhibitors should be used
7	Opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom NSAIDs, including COX 2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated
8	SYSADOA (glucosamine sulphate, chondroitin sulphate, ASU, diacerein, hyaluronic acid) have symptomatic effects and may modify structure
9	Intra-articular injection of long acting corticosteroid is indicated for flare of knee pain, especially if accompanied by effusion
10	Joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability

Table 7 Research agenda based on expert opinion

1	Clinical predictors of response to pharmacological and non-pharmacological interventions need to be determined
2	There is a need to establish a set of recommendations for uniform and full reporting of clinical trials in knee OA
3	Studies should include quality of life and function as well as pain, as outcome measures
4	New imagining techniques—that is, MRI and ultrasound require validation for the diagnosis and follow up of knee OA
5	Randomised controlled trials should more fully assess non-pharmacological interventions for knee OA
6	The most efficient and effective exercises need to be determined
7	What is the effect on tissue, efficacy, and safety of long term COX 2 inhibition
8	The clinical relevance of structural modification requires evaluation
9	The indications for joint replacement need to be determined
10	There is a need to examine the efficacy and cost utility of surgical techniques

initial oral analgesic for knee OA in published guidelines (ACR, RCP, EULAR). However, few studies have directly assessed the efficacy of paracetamol in knee OA and those that have are either of poor quality or have small patient numbers. A six week RCT in just 25 patients[41] (QS 21) showed a significant improvement in pain at rest with paracetamol compared with placebo. One four week RCT showed that paracetamol 4 g/day was as effective as ibuprofen (up to 2400 mg/day)[42] (QS 26). Re-evaluation of these data demonstrated that even severe knee pain responded equally to paracetamol and ibuprofen[43](QS 17). Another RCT showed that paracetamol could be used effectively in doses of up to 2600 mg/day for two years without significant adverse outcomes; it also showed that the efficacy of paracetamol was similar to that of naproxen 750 mg/day. This study had a high rate of withdrawals in both treatment arms, and the authors suggested that neither drug was satisfactory for the treatment of OA[44](QS 23). The issue of efficacy is clouded by the fact that most RCTs use paracetamol as escape analgesia, converting monotherapy trials to partial adjunctive studies. There are few drug interactions and no common contraindications to the use of paracetamol, including in the elderly.

In summary, there is evidence (1B) that paracetamol is effective in the treatment of knee OA and that in many patients it is comparable with ibuprofen in the short term and almost as efficacious as naproxen. There is also evidence (1B) that paracetamol can be taken safely over the long term. Clearly, a drug that is both safe and commonly effective should be considered early in the management of knee OA and, if effective, as an integral component of long term pain control.

There has been much recent controversy about the gastrointestinal safety of paracetamol, particularly as compared with NSAIDs. A recent editorial covers this issue well, with a review of the current available literature.[45] It concludes that currently the weight of clinical evidence supports the better overall gastrointestinal safety profile of paracetamol compared with non-selective NSAIDs.

5. Topical applications (NSAID, capsaicin) have clinical efficacy and are safe

Topical agents are commonly used, well tolerated and liked by patients. Two RCTs comparing topical diclofenac with placebo, in 70 and 155 patients respectively, recorded significant benefit over placebo for pain relief[46 47] (QS 24, 22). Interestingly, two RCTs comparing eltenac gel with placebo, involving 290 and 237 patients respectively, showed a significant improvement in pain relief only in those with severe knee OA[48 49] (QS 26, 25). Studies comparing diclofenac gel with ketoprofen gel[50](QS 19) and piroxicam gel with oral ibuprofen[51] (QS 20) showed equal efficacy between treatments. The ES for this form of treatment varies widely with a median ES of 0.31 (range −0.05 to 1.03). Topical NSAIDs have a good safety record. Large surveillance studies in general practice[52] suggest good safety (adverse events <1.5%) with local skin reactions the principal side effect, and one large case-control study has found no association between topical NSAIDs and upper gastrointestinal bleeding or perforation.[53]

Topical capsaicin (a treatment which reversibly desensitises nociceptive C fibres by acting on the VR-1 vaniloid receptors) is increasingly used in OA. There is good evidence for its efficacy in knee OA from an RCT, and it would appear its efficacy is maintained[54] (QS 21). ES ranges from 0.41 to 0.56. No systemic side effects are reported.

There is (1B) evidence for the efficacy and use of topical NSAIDs and capsaicin in the management of knee OA and these treatments have a good safety record.

6. NSAIDs should be considered in patients unresponsive to paracetamol. In patients with an increased gastrointestinal risk, non-selective NSAIDs and effective gastroprotective agents, or selective COX 2 inhibitors should be used

There is good evidence that NSAIDs are more efficacious than paracetamol for some patients, but the statement that they should be used in patients in whom paracetamol has failed, although attractive, does not have an evidence base. Unfortunately, there are no trials using failure of pain relief when treated with paracetamol as entry criteria for the trial.

With increasing focus on the low grade inflammatory component of OA, NSAIDs would appear to be logical drugs in patients unresponsive to paracetamol, particularly in the presence of clinically overt synovitis. However, there is no direct evidence base to support this statement. Numerous studies have shown that oral NSAIDs are better than placebo (ES median 0.50, range 0.47–0.96), confirming the efficacy of NSAIDs in the management of knee OA. A Cochrane review examining the relative efficacy of different NSAIDs used in knee OA concluded that despite the large number of publications in this area, many trials were poorly designed, and there was no evidence to distinguish between the efficacy of equivalent recommended doses of conventional NSAIDs.[55]

A few trials have directly compared paracetamol and NSAIDs. They have generally, but not exclusively, found that NSAIDs have better efficacy but increased gastrointestinal side effects. In a two year RCT[44] (QS 23) paracetamol was compared with naproxen in 178 patients. Naproxen led to greater reductions in pain than paracetamol (ES 0.32 after 42 days and 0.45 after 730 days). Patient drop out was high (65%) owing to lack of efficacy in the paracetamol arm and to adverse events in the naproxen arm. A further trial of 382 patients comparing rofecoxib, celecoxib, and paracetamol demonstrated that more patients discontinued treatment early with paracetamol because of lack of efficacy and that significantly more pain relief was obtained with the coxibs than with paracetamol; side effect profiles were similar for all treatment arms[56](QS 23).

There has been speculation that COX 2 selective agents are more beneficial than conventional NSAIDs, particularly in those at higher risk of adverse gastrointestinal side effects. Large trials comparing COX 2 inhibitors with placebo and conventional NSAIDs have shown their superiority over placebo and a similar efficacy to conventional NSAIDs for pain relief but with a reduction—up to 50%—in perforation, ulcers, and bleeding. An RCT comparing celecoxib, diclofenac, and placebo in 600 patients over six weeks showed that both drugs were better than placebo in improving pain but showed no difference between active treatments. There were more gastrointestinal side effects with diclofenac than celecoxib and the coxib was better tolerated[57] (QS21); there was an ES of 0.5 in comparison with placebo. A further study comparing varying doses of celecoxib with naproxen and placebo in 1003 patients found equal efficacy between the active treatment groups compared with placebo and an increased drop out rate in the placebo group due to lack of efficacy; in this study, however, the incidence of minor gastrointestinal related adverse events was similar for conventional NSAIDs and coxib, but one case of acute gastrointestinal bleeding occurred in the naproxen group[58](QS25). Current reports show that cardiorenal adverse events occur equally in patients treated with non-selective NSAIDs and coxibs.

A recent Cochrane review, including publications up to July 2002, examined the effectiveness of interventions for the prevention of NSAID induced upper gastrointestinal toxicity.[59] This included 40 RCTs and concluded that all doses of misoprostol significantly reduced the risk of endoscopic ulcers. Standard doses of histamine-2 receptor antagonists effectively reduced the risk of endoscopic duodenal but not gastric ulcers. Double doses of histamine-2 receptor antagonists and protein pump inhibitors effectively reduced the risk of endoscopic duodenal and gastric ulcers, and were better tolerated than misoprostol.

There is therefore (1A) evidence to support the use of NSAIDs in the treatment of knee OA. In those with an increased risk of gastrointestinal complications the evidence supports the use of either a COX 2 selective agent or the addition of a gastroprotective agent to a conventional NSAID.

7. Opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom NSAIDs, including COX 2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated

There is little direct evidence to fully support this statement. However, there is indirect evidence and the use of opioid analgesics is widely accepted in everyday clinical practice when other therapeutic options are limited. Indirect evidence would support that there is increased efficacy of pain control in those patients not entirely responsive to paracetamol and/or NSAIDs. It would be prudent, however, to counsel on the increased risk of adverse side effects, particularly in the elderly, and potential dependence when using this group of drugs. An RCT of 90 patients showed that treatment of knee OA with tramadol allowed reduction of the naproxen dose among those patients with naproxen-responsive pain[60] (QS 19). There is therefore (1B) evidence to support this statement.

8. SYSADOA (glucosamine sulphate, chondroitin sulphate, ASU, diacerein, and hyaluronic acid) have symptomatic effects and may modify structure

SYSADOA is a generic term used for symptomatic slow acting drugs for OA, and includes glucosamine sulphate and related compounds, chondroitin sulphate, and diacerein. There is wide variability throughout Europe in the use of these drugs and how they are classified. In the United Kingdom, for instance, they are classified as a health food supplement rather than a prescribable drug, are available only over the counter, and are very widely self administered. Those SYSADOA (for example, glycosaminoglycan polysulphates) that are no longer in use throughout Europe have not been included in this analysis. The other products have been assessed individually.

Both chondroitin sulphate and glucosamine sulphate have been the focus of a meta-analysis, including all studies up to 1999.[61] This report concluded that trials of chondroitin and glucosamine compounds demonstrated moderate to large effects on pain and disability in OA compared with placebo; however, these effects may have been exaggerated by publication bias. These products are also safe and associated with few side effects. The ES calculated for chondroitin sulphate was 0.78 and for glucosamine 0.44 in this meta-analysis, where they combined all the studies.

In an RCT assessing the efficacy of chondroitin sulphate compared with diclofenac in 146 patients, a prompter reduction of clinical symptoms was seen in patients treated with the NSAID, but these returned after the end of treatment; chondroitin, however, had a slower onset of action on the therapeutic response, but this lasted for up to three months after the end of treatment[62] (QS20). A more recent RCT[63](QS 27) demonstrated the benefit of chondroitin over placebo in 130 patients with knee OA and again showed persisting efficacy for up to one month after treatment.

Two RCTs have compared the effect of glucosamine sulphate with ibuprofen. The first, conducted over an eight week period, showed that ibuprofen was more effective at decreasing pain scores within the first two weeks of treatment, but at eight weeks, glucosamine sulphate was significantly better[64](QS 22). The second, conducted over four weeks, demonstrated that ibuprofen had a faster onset of action, but at four weeks the pain reduction and disability were similar[65](QS 23). Two other placebo controlled RCTs have been published in addition to those assessed in the meta-analysis. Ninety eight older patients with moderate to severe knee OA showed no difference in pain or function with glucosamine sulphate compared with placebo over a two month period[66] (QS 24). However, 106 patients with mild to moderate knee OA showed delayed progression of joint space loss and improvement in pain and function scores as compared with placebo over a three year period[67](QS 26). This had led to the suggestion that glucosamine sulphate could be used as a structure modifying agent in knee OA. Only one RCT has examined the efficacy of glucosamine and chondroitin sulphate in combination; in 93 patients, those with mild to moderate knee OA had significant improvement in the Lequesne index of knee severity score at four and six months; those with severe disease had no improvement over placebo[68](QS 24). An ES of 0.53–0.87 was calculated for glucosamine sulphate, excluding those used in the meta-analysis.

Only one RCT of diacerein in patients with knee OA was identified. At doses of 100 mg daily, significant differences in pain and handicap scores were seen compared with placebo. At higher doses, a significant number of adverse events were seen[69](QS 22).

The introduction of hyaluronic acid (HA) has been viewed as an advance in the management of knee OA. Its role in pain reduction, functional improvement, and in disease modification in knee OA has been assessed. Several HA preparations exist, in two main categories: high molecular and low molecular weight. It has been postulated that those preparations with a high molecular weight may have a superior effect. A 12 week RCT comparing a high molecular HA with a

low molecular HA showed that the higher molecular weight product was significantly better in relieving pain[70] (QS 21). Until February 2002, 39 trials have assessed the efficacy of HA for knee OA. Twenty trials assessed HA versus placebo and 18 of these were positive. RCTs that allowed calculation of ES recorded significant reductions in pain against placebo (ES 0.04, 0.49, 0.88, 0.9) over periods of 60 days to one year[71–74] (QS 22,19,23,14). One study recorded functional improvements on the Lequesne index (ES 0.36) over one year.[70]

Few trials have directly examined the effect on structure modification. One RCT looked at arthroscopic changes at baseline and after one year; less deterioration was seen over one year when treated with HA, and the HA group also scored higher for quality of life and reduced NSAID use during the period of study.[75] Another study demonstrated a reduction in the need for intra-articular steroid injections over a one year follow up period; the authors suggested a possible structure modifying effect by reducing flares.[71]

Studies examining possible predictors of response are few. Patients over 60 years with important functional impairment as documented by the Lesquesne index were associated with the greater efficacy of HA in one study[76](QS 26). A retrospective study found that the response to HA was statistically influenced by structural severity of the knee OA—those with less severe disease did better, and those with an effusion at baseline did worse[77](QS 18). It is noteworthy that most trials investigating intra-articular HA exclude severe OA.

In summary, there is evidence to support the efficacy of HA in the management of knee OA both for pain reduction (1B) and functional improvement (1B). However, although pain relief may be obtained for several months, rather than for several weeks as with steroid, this benefit may be offset by its slower onset of action and by the requirement of a course of 3–5 weekly injections with the logistical and cost issues that that entails. There is minimal evidence for a role in disease modification. The term SYSADOA covers a range of agents. There is growing evidence to support the use of two of these agents for their symptomatic effects—namely, glucosamine sulphate (1A) and chondroitin sulphate (1A), but for the others the evidence is weak or absent.

9. Intra-articular injection of long acting corticosteroid is indicated for flare of knee pain, especially if accompanied by effusion

Intra-articular corticosteroid injections in knee OA have been used to relieve pain and inflammation for many years. The effects of steroids in knee OA have been assessed in a number of studies. One RCT concluded that steroid was more effective than placebo for pain relief over seven days (ES 1.27) in patients with knee OA, not all of whom had effusions[78](QS 19). Another RCT involving 98 patients showed a significant difference in pain relief and functional outcomes between intra-articular steroid and placebo after one and four weeks but no difference at 12 and 24 weeks[79](QS 24). One RCT involving 84 patients confirmed short term symptom benefit of steroid over placebo and found a better outcome in those with an effusion[21](QS 22). However, a randomised crossover study of methylprednisolone versus saline found no clinical predictors of response, suggesting that steroid injection should not be reserved just for those with effusion alone[22](17).

In conclusion there is evidence (1B) that intra-articular injections of corticosteroid are effective but give relatively short lived benefit. The evidence for predictors of response, however, remains unclear and further studies are needed to answer this question.

10. Joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability

Joint replacement is an irreversible intervention used in those for whom other treatment modalities have failed and who generally have more severe disease. The effectiveness of total knee replacement (TKR) in knee OA has a well established place in those severely incapacitated. A systematic review concluded that TKR was a safe and effective treatment in improving quality of life,[80] as well as reducing pain and improving function. The evidence base to support this statement is built wholly on class 3 evidence from observational and retrospective analyses, often using prosthesis survival as the primary outcome measure.

A detailed review of surgery for knee OA identified 154 studies of 37 different tricompartmental prostheses in 9879 people (63% with osteoarthritis OA).[81] Good or excellent outcomes for pain and function were reported in 89% of people up to five years after surgery. Unicompartmental and bicompartmental prostheses were also reviewed and showed similar findings. The review concluded that all forms of knee replacement improve quality of life.

The general consensus among orthopaedic surgeons on indications for an operative procedure, carried out by a postal survey, were (*a*) severe daily pain and (*b*) *x* ray evidence of joint space narrowing.[82] There are no evidence based guidelines to support this, however.

No RCTs have compared TKR with non-surgical interventions. Although it is acknowledged that difficulties with study design may limit randomised studies on surgical treatments, there are areas that should be explored, including predictors of response, indications for joint replacement, and the effect of differences in surgical technique or joint prosthesis on long term outcomes. Moreover, postoperative outcome assessment should be carried out by an investigator independent of the surgeon who has performed the operation.

DISCUSSION

These clinical recommendations are based on the updated evidence obtained by reviewing the literature up to and including February 2002. The publication also seeks to accommodate all commonly used treatment modalities used in knee OA. The data collected and provided are restricted to the knee only, therefore, and those papers in which summary statistics could not be dissected from the other non-knee data were excluded. Equally, current recommendations cannot be extrapolated to OA at other sites.

The main purpose of the paper is to act as a resource document for secondary care, with the aim that each individual country should use the information generated to produce their own set of management guidelines and algorithms for treatment in primary care. As noted in the 2000 recommendations, there is often discordance between expert opinion and trial evidence, confirming that our own experience and local situations are important in determining individual treatment selection.

Reviewing the literature has reinforced the need to investigate predictors of response to individual treatments as the information relating to this important aspect is limited. Also, there is a lack of information about pooled/combination treatments, which would reflect everyday clinical practice. We still remain ignorant about the difference between efficacy (trial data) and clinical effectiveness (how useful in practice) for many of these treatments.

A heterogeneous array of outcome measures was used which makes comparison between different publications using the same treatment difficult. A more standardised

way of assessing the various treatments needs to be adopted internationally.

The task force attempted to review the evidence for efficacy of individual treatments and to give an additional more subjective summary of expert opinion on the overall safety and usefulness. The task force made no attempt to design a more didactic algorithm for management, even though it was realised that such a simplistic approach might have more immediate impact on the behaviour of health professionals. Many patient centred factors are important in determining the selection of treatments for individual patients with knee OA—for example, psychosocial factors and OA status; comorbid disease and drugs; patient beliefs about their knee OA; patient beliefs and preferences for its management; and previous patient experiences of treatments and health professionals. The costs and logistics of delivering specific interventions (for example, physiotherapy, weekly knee injections of HA) are also important. Therefore the management plan for patients with knee OA has to be individualised, reviewed, and adjusted in the light of the patient's response and adherence and will vary between patients and between locations. Optimistically, however, the findings of the current EULAR Recommendations show that there is a wide variety of treatments from which to choose for people with knee OA. There is no single right and wrong approach and each health professional must decide with each patient the most appropriate management plan at a particular time and for that location. It is hoped that discussion within healthcare provider groups of the treatment options outlined in this document will improve knowledge and interest in the management of knee OA and result in higher standards of care.

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Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

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EDITOR'S CHOICE

Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative

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ABSTRACT

Objectives: To develop evidence-based recommendations for the use of methotrexate in daily clinical practice in rheumatic disorders.

Methods: 751 rheumatologists from 17 countries participated in the 3E (Evidence, Expertise, Exchange) Initiative of 2007–8 consisting of three separate rounds of discussions and Delphi votes. Ten clinical questions concerning the use of methotrexate in rheumatic disorders were formulated. A systematic literature search in Medline, Embase, Cochrane Library and 2005–7 American College of Rheumatology/European League Against Rheumatism meeting abstracts was conducted. Selected articles were systematically reviewed and the evidence was appraised according to the Oxford levels of evidence. Each country elaborated a set of national recommendations. Finally, multinational recommendations were formulated and agreement among the participants and the potential impact on their clinical practice was assessed.

Results: A total of 16 979 references was identified, of which 304 articles were included in the systematic reviews. Ten multinational key recommendations on the use of methotrexate were formulated. Nine recommendations were specific for rheumatoid arthritis (RA), including the work-up before initiating methotrexate, optimal dosage and route, use of folic acid, monitoring, management of hepatotoxicity, long-term safety, mono versus combination therapy and management in the perioperative period and before/during pregnancy. One recommendation concerned methotrexate as a steroid-sparing agent in other rheumatic diseases.

Conclusions: Ten recommendations for the use of methotrexate in daily clinical practice focussed on RA were developed, which are evidence based and supported by a large panel of rheumatologists, enhancing their validity and practical use.

Methotrexate is the disease-modifying antirheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA) and is also used in other systemic rheumatic disorders.[1 2] Despite its widespread use and more than two decades of experience, considerable variation exists among rheumatologists in prescribing methotrexate, including the dosage, folic acid supplementation and safety monitoring.[3 4] In addition, little is known about the optimal management of methotrexate in specific clinical situations such as the perioperative period and before/during pregnancy. Existing guidelines often lack this level of detail.[5]

The 3E Initiative (Evidence, Expertise, Exchange) in rheumatology is a multinational effort, aimed at promoting evidence-based medicine, by formulating detailed recommendations addressing clinical problems.[6] In contrast to guidelines developed by a limited panel of experts, the 3E Initiative involves a broad international panel of practising rheumatologists. Furthermore, the initiative promotes epidemiology, by teaching and conducting systematic literature research following a strict methodology.[7]

Therefore, the objective of the 3E Initiative of 2007–8 was to develop practical recommendations for the use of methotrexate in rheumatic disorders, by integrating systematically generated evidence and expert opinion of a broad panel of international rheumatologists.

METHODS

A total of 751 rheumatologists from 17 countries participated in the 3E Initiative of 2007–8. Each country was represented by a scientific committee, consisting of one principal investigator and five to 16 members. The bibliographic team consisted of six international fellows (WK, EL, JAM-L, CS, JT, KV), three mentors (CB, LC, DvdH) and the scientific organiser (MD). During the first international meeting (n = 87 participants), 10 clinically relevant questions on the use of methotrexate in rheumatic disorders were formulated and selected by a Delphi vote. The areas addressed were, for RA: preadministration work-up, optimal dosage and route, use of folic acid, safety monitoring, hepatotoxicity (also for psoriatic arthritis (PsA)), long-term safety (>2 years), mono versus combination

therapy, management in the perioperative period and before/during pregnancy, and methotrexate as a steroid-sparing agent in other rheumatic disorders.

The bibliographic team conducted a systematic literature review, following the updated guidelines of the Cochrane Collaboration.[7] Each question was rephrased according to the PICO (population, intervention, comparison, outcome) method with the population defined as adult RA, PsA or other rheumatic diseases, and specific interventions, comparisons and outcomes defined according to each question.[8] Comprehensive search strategies were developed in collaboration with experienced librarians, including terms for methotrexate, RA and specific key words, without language restriction. Subsequently, Medline, Embase, Cochrane Library and European League Against Rheumatism (EULAR) 2005–7 and American College of Rheumatology (ACR) 2005–6 abstracts were systematically searched for articles published up to September 2007. Additional references were identified by a hand search. Articles were selected applying predefined inclusion and exclusion criteria and their methodological quality was graded according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine.[9] For each question, relevant data were extracted and appropriate statistics were calculated, including effect sizes, hazard ratios (HR), and standardised mortality ratios with 95% CI. If possible, meta-analyses were conducted using RevMan 4.2.10, calculating odds ratios (OR) with fixed effects and relative risks (RR) with a random effects model.

In the second round, a national meeting was held in each country (total n = 751 participants) to discuss the generated evidence and propose a set of recommendations. In a third joint meeting, the scientific committees (n = 94 participants) merged all propositions to 10 final recommendations by discussion and Delphi vote. The grade of recommendation according to the Oxford Levels of Evidence was assessed and the level of agreement was measured on a 10-point visual analogue scale (1, no agreement; 10, full agreement).[10] Finally, the potential impact among the participants was assessed using three statements: "this recommendation will change my practice"; "this recommendation will not change my practice as it is already my practice"; "this recommendation will not change my practice as I don't want to change my practice for this aspect".

RESULTS

A total of 16 979 references was identified, of which 304 articles were systematically reviewed (table 1). The 10 multinational key recommendations are listed in table 2, with the corresponding level of evidence and grade of recommendation. The mean level of agreement among the rheumatologists was 8.1 (range 7.4–8.8). The percentage of rheumatologists who indicated that they would change their clinical practice according to each recommendation is shown in table 3.

Table 1 Results of the systematic literature search for each recommendation topic

	Retrieved references by systematic literature search (n)	Articles included in the systematic reviews (n)
Pre-methotrexate work-up	1214	52
Dosage and route	1748	50
Folic acid	334	9
Monitoring	857	23
Hepatotoxicity	426	46
Long-term safety	2449	88
Mono vs combination	6958	20
Steroid-sparing agent	527	6
Perioperative period	303	4
Pregnancy	2163	6
Total	16 979	304

Recommendation 1

The work-up for patients starting methotrexate should include a clinical assessment of risk factors for methotrexate toxicity (including alcohol intake), patient education, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, complete blood count (CBC), creatinine, chest *x* ray (obtained within the previous year); consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.

The evidence needed to decide whether to start a patient with RA on methotrexate or not might be extrapolated from data on risk factors for severe toxicity. These data suggest that an estimated creatinine clearance of less than 79 ml/minute increases severe methotrexate (pulmonary) toxicity and that hypoalbuminaemia is associated with methotrexate-induced thrombocytopenia, liver and pulmonary toxicity.[11–15] In addition, lung abnormalities on radiographs, but not pulmonary function tests, are predictive of the development of methotrexate-induced pneumonitis.[16–18] Additional subgroups at risk of exacerbation of hepatic disease with methotrexate are obese patients, patients with diabetes and patients with viral or alcoholic hepatitis.[19–23] This observational evidence was combined with expert opinion, following from contraindications to methotrexate use frequently listed in randomised controlled trials (RCT) in RA from the past 15 years: significant renal disease, hepatic disorders, leucopenia less than 3.0×10^9/l, thrombocytopenia less than 100×10^9/l, age greater than 70 years, malignancy, pregnancy or inadequate contraception, history of alcohol/drug abuse, acute or chronic infection and pulmonary disease. Finally, four national recommendations from Austria, Germany, The Netherlands and Spain and the 1996 ACR guidelines on monitoring RA treatment, all suggest creatinine, CBC, AST/ALT with or without alkaline phosphatase, albumin, hepatitis B/C serology and a chest radiograph for the preadministration work-up.[24]

Recommendation 2

Oral methotrexate should be started at 10–15 mg/week, with escalation of 5 mg every 2–4 weeks up to 20–30 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in the case of inadequate clinical response or intolerance.

The results of three RCT directly comparing different dosages of oral methotrexate in RA showed dose-dependent efficacy and toxicity.[25–27] A starting dose of 25 mg/week compared with 15 mg/week was more effective, but with a trend towards more gastrointestinal toxicity.[26] Starting doses of 12.5–20 mg/week versus 5–10 mg/week resulted in higher clinical efficacy, without more toxicity.[25] Rapid dose escalation of 5 mg/month to 25–30 mg/week was associated with higher efficacy, but also with more adverse events, in comparison with slow escalation of 5 mg/3 months.[27] Regarding the optimal route of administration, retrospective studies suggest higher efficacy and less gastrointestinal toxicity with parenteral versus oral methotrexate,[28 29] which might be explained by the greater bioavailability of the parenteral form.[30 31] Indeed, the single RCT that compared 15 mg/week subcutaneous with oral methotrexate

Table 2 Multinational recommendations for the use of methotrexate in RA (1–7, 9–10) and other rheumatic disorders (8)

Recommendation		Level of evidence	Grade of recommendation	Agreement mean (SD)
1	The work-up for patients starting methotrexate should include clinical assessment of risk factors for methotrexate toxicity (including alcohol intake), patient education, AST, ALT, albumin, CBC, creatinine, chest *x* ray (obtained within the previous year); consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.	4	C	8.2 (1.9)
2	Oral methotrexate should be started at 10–15 mg/week, with escalation of 5 mg every 2–4 weeks up to 20–30 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in the case of inadequate clinical response or intolerance.	2b	B	7.8 (2.6)
3	Prescription of at least 5 mg folic acid per week with methotrexate therapy is strongly recommended.	1a–	A	7.5 (2.7)
4	When starting methotrexate or increasing the dose, ALT with or without AST, creatinine and CBC should be performed every 1–1.5 months until a stable dose is reached and every 1–3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.	4	C	8.1 (2.1)
5	Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the ULN, but may be reinstituted at a lower dose following normalisation. If the ALT/AST levels are persistently elevated up to three times the ULN, the dose of methotrexate should be adjusted; diagnostic procedures should be considered in the case of persistently elevated ALT/AST more than three times the ULN after discontinuation.	2b	C	7.4 (2.3)
6	Based on its acceptable safety profile, methotrexate is appropriate for long-term use.	2b	B	8.7 (1.9)
7	In DMARD-naive patients the balance of the efficacy/toxicity favours methotrexate monotherapy over combination with other conventional DMARD; methotrexate should be considered as the anchor for combination therapy when methotrexate monotherapy does not achieve disease control.	1a–	A	8.3 (2.1)
8	Methotrexate, as a steroid-sparing agent, is recommended in giant-cell arteritis and polymyalgia rheumatica and can be considered in patients with systemic lupus erythematosus or (juvenile) dermatomyositis.	1b	B	7.7 (2.1)
9	Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.	1b	B	8.8 (1.9)
10	Methotrexate should not be used for at least 3 months before planned pregnancy for men and women and should not be used during pregnancy or breast feeding.	4	C	8.2 (2.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; ULN, upper limit of normal.

showed greater clinical efficacy, but also more withdrawal as a result of toxicity with subcutaneous methotrexate in early methotrexate-naive RA patients.[32] In contrast, in RA patients who failed methotrexate 15–20 mg/week plus other DMARD, neither a switch to 15 mg/week administered intramuscularly, nor subsequent dose escalation resulted in increased efficacy.[33] In conclusion, the experts preferred the oral route, dosed according to the recommendation, with a possible switch to parenteral in case of an insufficient response at the highest tolerable dose.

Recommendation 3

Prescription of at least 5 mg folic acid per week with methotrexate therapy is strongly recommended.

A meta-analysis of nine studies including 788 RA patients suggested that folic acid supplementation reduces gastrointestinal and liver toxicity of methotrexate, without reducing efficacy.[34] Four studies using folic acid 7–35 mg/week showed a significant reduction in the risk of gastrointestinal side effects (OR 0.42; 95% CI 0.21 to 0.85),[35–38] in contrast with only one study using 5 mg/week folic acid, which did not reach significance.[37] After further stratification, however, the protective effect was only significant in the two studies that used methotrexate at less than 10 mg/week (OR 0.21; 95% CI 0.07 to 0.69)[36 37] and not in the two largest studies using methotrexate 14–18 mg/week (OR 0.61; 95% CI 0.25 to 1.48).[35 38] The two studies in which hepatotoxicity was analysed showed a significant protective effect with 1 mg/day folic acid (OR 0.17; 95% CI 0.09 to 0.32], irrespective of the methotrexate dose.[35 36] Only folinic acid at doses of 5 mg/week or less significantly decreased gastrointestinal side effects and hepatotoxicity (OR 0.39; 95% CI 0.2 to 0.76 and OR 0.16; 95% CI 0.09 to 0.29, respectively).[35 39–41] Furthermore, folinic acid at greater than 5 mg/week was associated with a significant increase in

Table 3 Percentage of rheumatologists in the 3E Initiative who indicated for each recommendation if it would change their clinical practice

Recommendation (number and topic)		The recommendation will change my practice (%)	The recommendation is already my practice (%)	I don't want to change my practice for this aspect (%)
1	Pre-methotrexate work-up	29.8	61.2	9.0
2	Dosage and route	16.2	68.7	15.1
3	Folic acid	15.3	78.6	6.1
4	Monitoring	21.1	53.5	25.4
5	Hepatotoxicity	16.5	68.0	15.5
6	Long-term safety	2.0	96.0	2.0
7	Mono vs combination	5.0	86.9	8.1
8	Steroid-sparing agent	25.6	67.1	7.3
9	Perioperative period	41.3	46.7	12.0
10	Pregnancy	19.5	71.3	9.2

the number of tender and swollen joints (OR 6.27; 95% CI 1.64 to 10.90 and OR 5.3; 95% CI 0.03 to 10.58, respectively), whereas folic acid or low dosages ($\leq$5 mg/week) of folinic acid were not.[39 42 43] In conclusion, the experts favoured folic acid and recommended at least 5 mg/week, taking into account the potential need for higher dosages, with the currently higher dosed methotrexate.

Recommendation 4

When starting methotrexate or increasing the dose, ALT with or without AST, creatinine and CBC should be performed every 1–1.5 months until a stable dose is reached and every 1–3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.

Both the mean AST and the percentage of elevated AST have been reported to correlate with histological grades of liver disease in RA.[15 44–47] The 1994 ACR guidelines for monitoring hepatotoxicity showed 80% sensitivity and 82% specificity for detecting fibrosis/cirrhosis of serial abnormal AST tests, with fewer costs and complications compared with routine liver biopsy.[48 49] One study suggests that ALT alone might detect 90% of the elevated AST or paired tests.[50] In contrast, alkaline phosphatase seems oversensitive for monitoring hepatotoxicity.[48] In addition to transaminases, renal function should be monitored, as it is associated with increased (pulmonary) toxicity and CBC is required to monitor haematological toxicity.[11 51] Less evidence is available on the frequency of monitoring, although two observational studies showed an optimal interval for identifying abnormal liver enzymes of 30–60 days and a decreasing incidence of abnormal liver enzymes in the first months of methotrexate therapy.[48 52] Accordingly, the four national recommendations and the 1996 ACR guidelines suggest monitoring every 1–3 months, with initially more frequent assessments.[24]

Recommendation 5

Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the upper limit of normal (ULN), but may be reinstituted at a lower dose following normalisation. If the ALT/AST levels are persistently elevated up to three times the ULN, the dose of methotrexate should be adjusted; diagnostic procedures should be considered in the case of persistent elevated ALT/AST more than three times the ULN after discontinuation.

Pooled data of 2062 RA patients after a mean of 3.3 years on methotrexate showed that the cumulative incidence of abnormal ALT/AST was 48.9% above the ULN and 16.8% above two to three times the ULN.[53] Methotrexate was frequently continued without a dose change, but the frequency of (spontaneous) normalisation was insufficiently reported. In addition, pooled percentages of mild and severe fibrosis and cirrhosis in 1113 RA patients after a mean of 4.1 years on methotrexate were 15.3%, 1.3% and 0.5%, respectively. However, the results of pre-methotrexate biopsies already showed a prevalence of 9.1% mild fibrosis and 0.3% cirrhosis.[53] For PsA, a somewhat higher incidence of elevated liver enzymes and fibrosis/cirrhosis compared with RA was found, but the evidence is very limited.[21 54–57] For RA, the evidence suggests that liver enzyme elevation is frequent but often transient, that multiple rather than single findings associate with an abnormal biopsy (as noted earlier) and that methotrexate-induced fibrosis/cirrhosis is rare. The experts emphasised considering other causal factors, including non-steroidal anti-inflammatory drugs, obesity and alcohol and other diagnostic procedures than liver biopsy in the case of persistently elevated liver enzymes after the discontinuation of methotrexate.[22 44 58]

Recommendation 6

Based on its acceptable safety profile, methotrexate is appropriate for long-term use.

RA patients have an increased mortality rate compared with the general population (standardised mortality ratio 1.9; 95% CI 1.3 to 2.8).[59] However, RA patients on methotrexate compared with patients without methotrexate had a lower mortality incidence rate (23/1000 versus 26.7/1000 patient-years) and reduced cardiovascular mortality (HR 0.3; 95% CI 0.2 to 0.7) in a large 6-year prospective study.[60] In addition, in two case–control studies, methotrexate was not a risk factor and even reduced the risk of cardiovascular disease, respectively (OR 0.11; 95% CI 0.02 to 0.56).[61 62] In a meta-analysis and several cohorts with 5–12 years follow-up, methotrexate was less often discontinued because of toxicity than other DMARD, except for hydroxychloroquine.[63 64] Gastrointestinal events and elevated liver enzymes are the most frequently encountered toxicities.[64] However, as discussed earlier, the risk of severe fibrosis and cirrhosis seems low. Long-term methotrexate use was not associated with an increased risk of serious infections (HR 0.91; 95% CI 0.57 to 1.45), including herpes zoster (HR 1.0; 95% CI 0.8 to 1.3).[65 66] Although RA patients have an increased risk of lymphoma compared with the general population, evidence on the risk of methotrexate use independent of RA is inconclusive, because studies did not address RA as the reference population and the risk was not adjusted for disease severity.[67 68] Five case reports suggest that methotrexate might be associated with Epstein–Barr virus-related lymphoproliferative disease and regression after methotrexate withdrawal.[69–73]

Recommendation 7

In DMARD-naive patients the balance of efficacy/toxicity favours methotrexate monotherapy over combination with other conventional DMARD; methotrexate should be considered as the anchor for combination therapy when methotrexate monotherapy does not achieve disease control.

A meta-analysis of 20 RCT evaluated methotrexate mono versus combination therapy in RA, excluding combinations with corticosteroids or biological agents.[74] Analyses were stratified for DMARD-naive patients and patients with an inadequate response to previous methotrexate or other DMARD. Methotrexate combination therapy was superior to methotrexate monotherapy mainly in patients with a previous inadequate response to methotrexate, resulting in significantly more ACR20 (RR 2.51; 95% CI 1.92 to 3.28), ACR50 (RR 4.54; 95% CI 2.51 to 8.2) and ACR70 (RR 5.59; 95% CI 2.08 to 15.01) responses.[75–78] In contrast, in patients who failed other DMARD, only significantly more ACR20 responses (RR 1.85; 95% CI 1.21 to 2.83) were seen with combination therapy and a trend for more EULAR good response and remission.[79 80] In DMARD-naive patients, combination therapy showed a trend for more EULAR moderate response and remission, but only ACR70 responses were significantly more often achieved (RR 2.41; 95% CI 1.07 to 5.44).[81–85] Regarding toxicity, methotrexate combined with sulfasalazine and methotrexate combined with leflunomide each significantly increased the risk of gastrointestinal side effects and hepatotoxicity, with a trend towards more withdrawal as a result of toxicity.[76 79 81 82 86 87] In contrast, methotrexate combined with sulfasalazine and hydroxychloroquine

did not increase the risk of withdrawal due to toxicity.[88] Weighing efficacy and toxicity, the experts favoured methotrexate monotherapy over the combination with conventional DMARD in DMARD-naive RA patients. As such, the recommendation does not contradict the well-established superiority of combination therapies including either prednisone or anti-tumour necrosis factor.[89–92]

Recommendation 8

Methotrexate, as a steroid-sparing agent, is recommended in giant-cell arteritis and polymyalgia rheumatica and can be considered in patients with systemic lupus erythematosus or (juvenile) dermatomyositis.

An individual patient data meta-analysis evaluated the steroid-sparing effect of methotrexate 7.5–17.5 mg/week versus placebo in giant-cell arteritis patients on high-dose prednisone.[93] The results showed a higher prednisone discontinuation rate (HR 2.84; 95% CI 1.52 to 5.28), significantly lower cumulative steroid dose and fewer relapses with methotrexate therapy after 1 year. Two RCT in polymyalgia rheumatica also showed significantly more prednisone discontinuation with methotrexate 10 mg/week compared with placebo, significantly fewer relapses and a trend towards lower prednisone duration and cumulative dose.[94 95] Systemic lupus erythematosus patients in two RCT evaluating methotrexate 7.5–20 mg/week versus placebo had significantly more prednisone reduction, fewer skin and joint flares, but more adverse events with methotrexate therapy.[96 97] Finally, in a cohort study, juvenile dermatomyositis patients discontinued prednisone significantly earlier and had significantly lower cumulative prednisone doses with concomitant methotrexate therapy, but without an additional beneficial effect on disease activity.[98] No studies were found comparing the steroid-sparing effect of methotrexate with other DMARD.

Recommendation 9

Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.

Four studies evaluated stopping or continuing methotrexate one or more weeks before elective orthopaedic surgery in RA. In one RCT, no differences in postoperative complications were observed between patients who continued or stopped methotrexate (mean dose 10 mg/week).[99] In a second RCT, patients who continued methotrexate (mean dose 10 mg/week) reported significantly fewer RA flares than patients who stopped methotrexate.[100] In contrast, in a prospective cohort study postoperative infections occurred in 30% of patients who continued methotrexate compared with none of the patients who stopped methotrexate, without postoperative flares of RA in either group.[101] However, a multivariate analysis in another cohort study showed that the perioperative use of methotrexate was not associated with wound morbidity ($p = 0.84$) and significantly reduced RA flares.[102] Although these studies suggest that methotrexate can be safely continued in the perioperative period of elective orthopaedic surgery, no studies were found regarding (non-)elective non-orthopaedic surgery.

Recommendation 10

Methotrexate should not be used for at least 3 months before planned pregnancy for men and women and should not be used during pregnancy or breast feeding.

Six studies assessed the outcome of continued methotrexate therapy before/during pregnancy in (mostly) RA patients by surveys and database searches.[103–108] A total of 101 pregnancies was exposed to methotrexate during pregnancy (n = 92) or before conception (n = 9). Eighteen induced abortions were reported, but the reasons were not stated. A total of 20 (24%) miscarriages, five (6%) congenital malformations and 62 (75%) live births was reported, with one (1%) patient lost to follow-up. In healthy women, corresponding percentages are 12–16% miscarriages and 3–5% congenital malformations.[109 110] In contrast, no studies were found that evaluated the effect of methotrexate for men on miscarriages/birth defects, male and female fertility or on newborns during lactation. Nevertheless, expert opinion is to stop methotrexate at least 3 months before planned pregnancy in both men and women and not to use methotrexate during pregnancy or breast feeding.

DISCUSSION

Ten multinational recommendations for the use of methotrexate in daily clinical practice were developed, which are practical, evidence-based and supported by a large panel of international rheumatologists in the 3E Initiative.

The involvement of 751 rheumatologists from 17 countries was unique in the development of the current recommendations. It allowed a selection of relevant topics, reflecting frequently encountered questions on the use of methotrexate in daily practice. Furthermore, a broad participation increases external validity and enhances future dissemination and implementation into rheumatological practice worldwide.

A second principal feature of the initiative was the systematic literature research. Following a strict methodology, we aimed to find all available evidence regarding each topic, which resulted in a large number of reviewed articles. Although for some areas little to no evidence was found, including (the frequency of) toxicity monitoring, the timing of folic acid, non-orthopaedic surgery and the effect of methotrexate on fertility and lactation, the majority of the recommendations is supported by evidence from RCT and high-quality cohort studies.

The same evidence, however, might limit the recommendations, as many studies were old and included longstanding RA patients who received methotrexate in low dosages without folic acid. As this may not reflect current clinical practice, the results should be interpreted and extrapolated with caution. In addition, patients' participation and preferences may influence the recommendations. Nevertheless, the recommendations are based on currently available evidence and can be adjusted if future studies or clinical experience reveal new insights.

In summary, multinational recommendations for the use of methotrexate in daily clinical practice focussed on RA were developed, integrating systematic literature review and expert opinion, with the aim of promoting evidence-based medicine and ultimately improving patient care.

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Rheumatology Therapeutics: Drugs and Biologics

This table lists the FDA-approved therapeutics (biologics and drugs) for rheumatologic diseases and conditions; it does not list some FDA-approved devices and over-the-counter medications. For an explanation of the Indications (i.e. disease or condition), please see Information on Rheumatology Drugs by Disease or Condition.

- The drugs listed in italics have links to Drugs@FDA, but there is no label at this site.
- The drugs listed in bolded italics are not listed in Drugs@FDA.
- All other drugs and biologics have labeling available at Drugs@FDA.

Indications

AS - Akylosing Spondylitis B - acute and subacute Bursitis B&T - Bursitis and Tendinitis CAPS - Cryopyrin-associated Periodic Syndromes DM - Dermatomyositis E - Epicondylitis FM - Fibromyalgia	G - Gout KS - Kawasaki Syndrome JIA - Juvenive Idiopathic Arthritis (Juvenile Rheumatoid Arthritis) OA - Osteoarthritis PMR - Polymyalgia Rheumaticia PM - Polymyositis PsA - Psoriatic Arthritis	RA - Rheumatoid Arthritis RP - Relapsing Polychondritis SS - Sjogren's Syndrome SysS - Systemic Sclerosis SLE - Systemic Lupus Erythematous T - acute non-specific Tenosynovitis V - Vasculitis

Approved Rheumatology Therapeutics

Generic Name and Drug Category	Brand Name	Indication(s)
Abatacept	Orencia	RA
Adalimumab	Humira	AS, RA, PsA
Allopurinol	Zyloprim	G
Ambrisentan	Letairis	Pulmonary hypertension in SysS
Anakinra	Kineret	RA
Aspirin	Ecotrin	RA, OA, AS, PsA, JIA, SLE
Auranofin	***Ridura***	RA
Aurothioglucose	***Solganal***	RA, JIA
Azathioprine	Imuran	RA, JIA
Bosentan	Tracleer	Pulmonary hypertension in SysS
Celecoxib	Celebrex	OA, RA, JIA
Cevimeline	Evoxac	SS
Colchicine	***Colchicine***	G

Cyclosporin	Neoral	RA
Duloxetine Hydrochloride	Cymbalta	FM
Epoprostenol sodium	Flolan	Pulmonary hypertension in SysS
Etanercept	Enbrel	AS, RA, JIA, PsA
Gold sodium thiomalate	***Myochrysine***	RA, JIA
Hydroxychloroquine Sulfate	Plaquenil	RA, SLE
Hylan G-F 20	***Synvisc***	OA
Illoprost	Ventavis	Pulmonary hypertension in SysS
Infliximab	Remicade	AS, RA, PsA
Intravenous Immunoglobulin	***Gammagard S/D***	KS
Leflunomide	Arava	RA
Methylprednisolone acetate	Depo-Medrol	OA, RA, G, PsA, AS, B&T
Methotrexate	***Rheumatrex*** Trexall	RA, JIA
Non-Selective NSAIDs	See NSAID table	RA, OA, AS, JIA, G, PsA
Penicillamine	Cuprimine	RA
Pilocarpine	Salagen	SS
Prednisolone *Prednisone*	Corticosteroids	AS, B&T, DM, G, JIA, PM, PMR, PsA, RA, RP, SLE, SS, V
Pregabalin	Lyrica	FM
Probenecid	Benemid	G
Probenecid & ***colchicine***	ColBenemid	G
Rilonacept	Arcalyst	CAPS

Rituximab	Rituxan	RA
Sodium hyaluronate	http://www.accessdata.fda.gov/cdrh_docs/pdf/p950027.pdf	OA
Sulfasalazine	Azulfidine Azulfidine EN-Tabs	RA, JIA
Sulfinpyrazone	*Anturane*	G
Triamcinolone acetonide	Kenalog	OA, RA, G, PsA, AS, B&T
Triamcinolone diacetate	Aristospan	OA, RA, G, PsA, AS *discoid lupus, cystic tumors of an aponeurosis or tendon*

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Glucosamine/chondroitin/primorine combination therapy for osteoarthritis.

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Osteoarthritis (OA) is the most common arthritis affecting the aging population. This degenerative disease can cause significant pain and functional disability in affected individuals. Despite advances in the retardation of rheumatoid arthritis with disease-modifying agents, comparable oral agents have been relatively unavailable for OA. The mainstays of therapy continue to be acetaminophen and nonsteroidal antiinflammatory medications to manage symptoms. Unfortunately, these medications can precipitate severe adverse events in some patients or may be contraindicated, leaving few choices remaining to control pain and suffering. Glucosamine sulfate and chondroitin sulfate have been evaluated in many studies as agents to relieve pain, improve functional activity, and slow disease progression in OA especially of the hip and knee. Studies have reported conflicting results regarding improvement in the pain and disability associated with OA with the use of glucosamine and chondroitin as single agents; however, when improvement has been demonstrated, the formulation has primarily been glucosamine sulfate combined with chondroitin sulfate. Recently, as a result of information implicating the role of reactive oxygen species and oxidative cellular stress reactions on the onset of neurodegenerative and inflammatory disorders, it has been theorized that medications that could control or alter these reactions might improve or prevent the onset of these conditions. Primorine is a combination of products thought to alter these biochemical oxidative byproducts. Based on current evidence, the use of a combination product of glucosamine sulfate and chondroitin sulfate seems to have the greatest potential as a therapeutic intervention for patients at increased risk from the adverse events of accepted current oral therapies. The use of primorine and its combination of products as an intervention in OA has theoretical advantages but its benefits are unproven. A new product, relamine, is a combination of these three formulations. While no studies have evaluated glucosamine sulfate, chondroitin sulfate and primorine in a single product, it may be an option for those who wish to try an alternate therapy for OA, as there appears to be a low risk for serious adverse events.